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Research Advances

SEALANTS TESTED FOR IMPROVED RETENTION

Plastic sealants, which are applied to chewing surfaces of the teeth to prevent decay, should become more effective as a result of research conducted by scientists at the University of Michigan, Ann Arbor.

Previous studies have shown that some sealants are more secure than others, depending on the operator's application procedure. The new research, supported by the National Institute of Dental Research, shows improved sealant retention when two factors, previously unstressed, are taken into consideration.

The first factor concerns air bubbles trapped in tooth fissures. The investigators report less air trapped when the liquid is applied with a brush at one edge of the tooth and allowed to flow smoothly to the other edge.

The second important factor is the sealant's viscosity. Thicker solutions, whose coefficient of penetration is 0.24 cm/sec or less, permeated no more than 65 percent of narrow fissures a minute after application. This is approximately the time it takes the plastic to harden or polymerize under long-wave ultraviolet light.

Previous research has shown that shallow, wide-mouthed fissures are usually filled by sealants, whereas deep, narrow fissures tend to fill incompletely. However, the University of Michigan scientists found that if they avoided trapping air bubbles, sealant mixtures with high penetration coefficients (above 0.24 and up to 1/31 cm/sec) always filled narrow fissures.

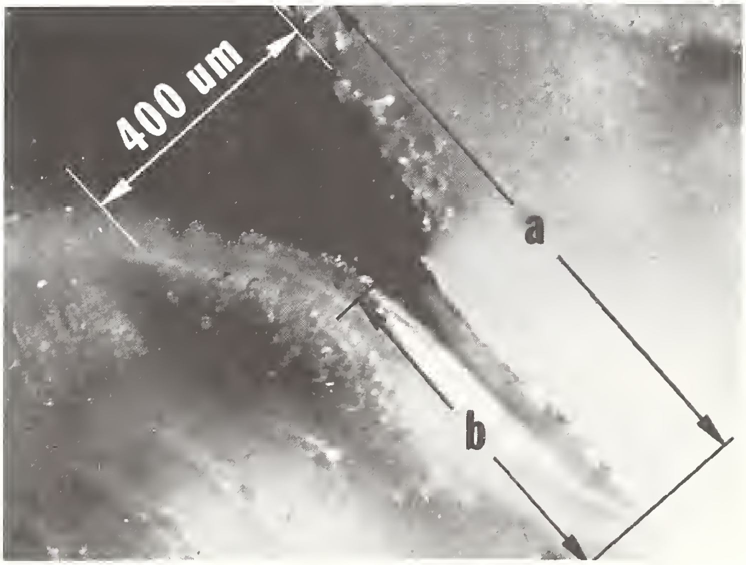
The investigators cut sections through extracted human teeth selected for deep, narrow fissures, and sealed them with transparent tape as test preparations. In these fissures, they compared the performance of four formulations of

SEALANTS (Cont'd)

the basic BIS-GMA resin diluted with methylmethacrylate and colored with dye. This made it easier to observe, photograph, and measure penetration of the sealant. The researchers did not add the polymerization chemical to the solution, enabling the tested sealant to be easily removed. After it was removed, the section was cleaned ultrasonically, and the same fissure could be used repeatedly for accurate comparison of the performance of the various sealant mixtures at 23° C.

The penetration coefficient of a sealant can be determined by a glass capillary method. It is possible to use penetration coefficients to set up standards in sealant performance.

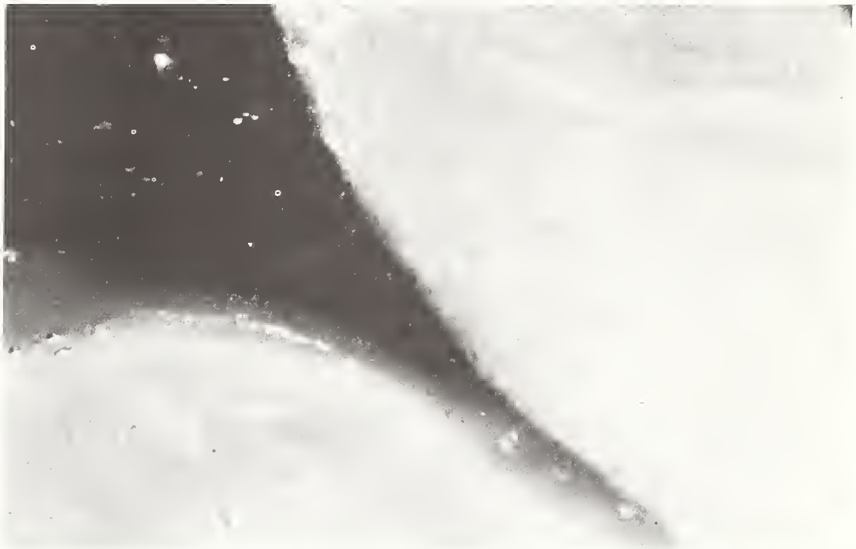
Alexis A. Apostolidis, D.D.S., William J. O'Brien, Ph.D., and Pui L. Fan, Ph.D., reported their study at the April, 1975, meeting of the American Association for Dental Research in New York City.



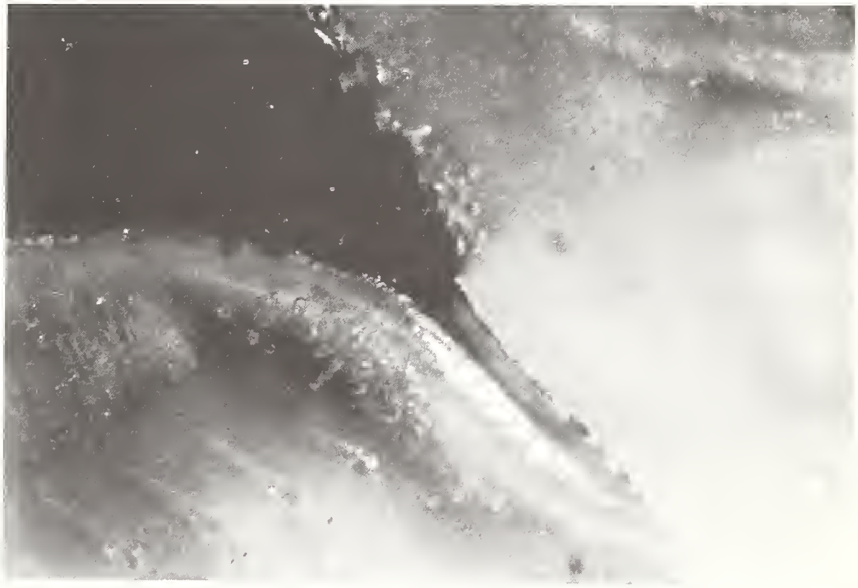
This photomicrograph of a human tooth illustrates the calculation of sealant penetration. This view is a length-wise cut through a deep tooth fissure. The top of the fissure is 400 micrometers wide and about 900 micrometers long. The percentage of sealant penetration equals 100 times a - b divided by a. (NIH Photo #1407)

(more)

SEALANTS (Cont'd)



The top photograph of a human tooth fissure sliced in half shows complete filling with dye-tinted sealant. (NIH Photo #1408)



In the bottom photograph, the same fissure is shown incompletely filled by a dye-tinted sealant too viscous to penetrate its narrowest depths. (NIH Photo #1409)

#

Note to Subscribers

Ms. Nancy Zimmerman, an NIH summer journalism intern and student in medical communications at Ohio State University, prepared this story and assisted in the preparation of other stories in this issue.

#

Research Advances

HUMAN IMMUNE SYSTEM MAY PROVIDE CANCER INDICATOR

The human body's immune system may prove effective in screening populations and high risk groups for the presence of cancer, reported Ronald B. Herberman, M.D., at the May 1975 meeting of the National Conference on Advances in Cancer Management, held in Denver.

The immune system, which defends against disease, may also prove effective in monitoring the course of cancer treatment, and providing a means for early detection of metastatic spread of cancer.

Dr. Herberman, chief of the National Cancer Institute's (NCI's) Laboratory of Immunodiagnosis, discussed immunologic tests for cancer at the conference, cosponsored by NCI and the American Cancer Society.

The ideal test for detection and diagnosis of cancer would be specific for any type of cancer in all body sites, Dr. Herberman said. In addition, the test would be specific only for cancer and not give positive reactions to noncancerous conditions.

Although such ideal tests have not yet been developed, tests with less accuracy could also be very useful. Several tests may be used together, for example, each one capable of identifying only a portion of people with a specific form of cancer.

Further, the substance monitored by an immunologic reaction does not have to be specific to cancer but may be present as well in healthy people and in people with benign conditions. If the level of the substance were found above or below the amount found in healthy individuals, cancer could be indicated.

The NCI scientist described certain immunologic procedures that may prove

(more)

useful. Tumors may release characteristic antigens into the bloodstream of the host. An antigen is a substance that can stimulate an immune response such as formation of antibodies in the host or in animals injected with the substance. One such antigen, the subject of a great deal of research, is carcinoembryonic antigen (CEA). A test for CEA is being used in combination with other medical procedures for the diagnosis and management of several forms of cancer.

One of the major efforts of the NCI Immunodiagnosis Contract Program, said Dr. Herberman, is to determine the further value of the CEA test and to develop similar tests. Scientists at the Scripps Clinic Research Foundation, La Jolla, California, with support from NCI, have isolated a chemical fraction of CEA, called CEA-S. This fraction appears to be more specific than CEA for cancer detection, especially colon cancer and other cancers of the gastrointestinal tract. Other promising antigens are being sought.

Tests that measure cellular immune responses also may be used to diagnose cancer. Many cancer patients have deficient immune systems, as shown by low levels of T lymphocytes, white blood cells responsible for seeking out and destroying foreign tissues in the body. The level of a patient's cellular immune activity may be measured by skin tests similar to the test for tuberculosis. An antigen prepared from cells of a specific type of cancer, said Dr. Herberman, can cause a local reaction when injected under the skin. Research on such tests began only a few years ago, however, and further studies are needed before their value is known.

Tests are being developed to measure the patient's reactivity against tumor antigens. One such test, the lymphocyte stimulation test, measures the activation (specifically, cell division) of a patient's lymphocytes when they

(more)

IMMUNE SYSTEM (Cont'd)

are exposed to a tumor antigen. Another test measures the inhibition of leukocyte migration. In the presence of an antigen to which the patient is immune, white blood cells will slow their movements. Both tests are conducted with blood samples in the laboratory.

Other scientists are studying antibodies tagged with radioactive markers. The research may lead to use of tagged antibodies as a follow-up to other diagnostic tests that indicate the presence of cancer but fail to pinpoint the location. Once a tumor is known to exist, tagged antibodies would be injected and move directly to the tumor. Scanning techniques, such as are now used for bone, liver and thyroid studies, would be able to trace the antibodies and locate the tumor.

#

COLLATERAL CIRCULATION--Nature has her own remarkable way of averting disaster even though the coronary arteries have started to harden--"collateral circulation." Neighboring arteries carry more blood than formerly to compensate for a narrowed vessel, and new arterial branches open up to help transport blood to where it is needed, according to the National Institutes of Health.

COMPUTERS--Computers at the National Institutes of Health can monitor a post-surgery patient's heart rate and blood pressure 200 times a second.

#

Research Advances

Animal Studies...

PRIOR BLOOD TRANSFUSIONS RISK BONE MARROW GRAFT'S SUCCESS

Animal studies by National Institute of Allergy and Infectious Diseases grantees in Seattle have shown that blood transfusions from a bone marrow transplant donor, as long as three months prior to the transplant, significantly increase the chance of the graft's rejection. Irradiating the recipient shortly before the transplant and using immunosuppressive therapy afterwards have failed to overcome this effect.

Human bone marrow transplants reconstitute bone marrow production of cells in patients whose marrow has stopped functioning due to disease, radiation accidents, or treatment for certain types of malignancies, such as leukemia. One transfusion ten days prior to the transplant is known to jeopardize the graft's success, but the very nature of the patient's problem usually requires some form of blood transfusion prior to transplantation.

The Seattle group decided to further investigate the effects of prior blood transfusion on sensitization of bone marrow recipients. In their studies, the scientists paired unrelated dogs of different breeds and opposite sex. These animals, with mismatched histocompatibility antigens, were given a blood transfusion from their prospective donors either 24 hours or three months before the transplant.

Four hours before the transplant, each animal received a lethal dose of total body irradiation (1200 rads) to prevent its immune response from destroying the graft. For the same reason, each dog also received an immunosuppressive drug, methotrexate, after the graft.

(more)

TRANSFUSIONS (cont'd)

Animals who received blood three months before the transplant had a significantly higher incidence of grant rejection (50 percent) than did a composite group of untransfused dogs (16 percent). Those animals transfused 24 hours prior to irradiation and grafting had the highest number of rejections (86 percent).

The scientists believe that exposure to histocompatibility antigens, presumably on platelets and white cells in a whole blood transfusion, may sensitize the recipient and result in the graft rejection. Rejection despite irradiation complements other studies which have found that irradiation is most effective as an immunosuppressive agent when it is given before antigen exposure.

The results of this study confirm the relationship of prior transfusion to graft rejection, a major problem in human bone marrow transplantation. Since candidates for transplants will continue to need supportive blood transfusion before a transplant, methods must be developed to overcome this sensitization.

Currently, this detrimental effect of prior transfusions is restricted to bone marrow transplants. Prior transfusion appears to promote the acceptance of kidney transplants in humans and in rats.

The Seattle researchers -- P. L. Weiden, M.D., R. Storb, M.D., H. J. Kolb, M.D., T. C. Graham, M.D., G. Kao, M.D., and E. D. Thomas, M.D., at the University of Washington School of Medicine, the U. S. Public Health Service Hospital, Harborview Medical Center, and Providence Medical Center -- reported their findings in the March, 1975 issue of *Transplantation*.

#

Research Advances

ANTIBODIES SUPPRESS HYPERSENSITIVITY

Delayed hypersensitivity, an immunologic reaction, causes harmful rejection of kidney grafts and poison ivy reaction, and affects the protective cellular immunity against most forms of cancer and many infectious diseases. This condition also causes such self-destroying autoallergic illnesses as post-infection encephalitis, a close relative of multiple sclerosis. The control of delayed hypersensitivity is therefore very important, biologically and medically.

The body protects itself against autoallergic self-destruction through very specific active mechanisms that carefully control delayed hypersensitivity and cellular immunity. These mechanisms have high specificity because they are immunologic; therefore, certain kinds of immunologic responses control other kinds of immunologic responses.

One response which regulates the induction of delayed hypersensivitity is affected by a serum antibody. This antibody, which provides us with specific immunity to diphtheria, tetanus, pneumonia, and poliomyelitis, resembles the immunoregulatory antibody, but critical analyses show they are not the same. Evidence suggests that the immunoregulatory antibody is intended by nature to oversee and help direct the body's immunologic responses.

Investigators at the Webb-Waring Lung Institute in Colorado studied the mechanisms of immunoregulation in inbred strains of mice. They induced delayed hypersensitivity to simple, purified proteins and stimulated the mice to make immunoregulating serum antibodies against the proteins which prevent the development of delayed hypersensitivity.

(more)

HYPERSENSITIVITY (Cont'd)

The antibodies belong to a class of mouse serum immunoglobulins known as IgF or $7S\gamma_1$, but paradoxically, most of the antibodies belonging to this class do not immunoregulate. The researchers found that immunoregulation is a property only of antibodies in this class that have the strongest negative charge and therefore migrate farthest away from the cathode in an electrophoretic field.

They demonstrated this by making precipitating antibodies in a rabbit which reacted solely with the immunoregulatory antibodies. With the rabbit antiserum, they showed that mouse antisera rich in these "contrasensitizing" (preventing sensitization) antibodies have expected high concentrations of this subclass of immunoglobulin. They removed some contrasensitizing activity from mouse antiserum by mixing it with the rabbit antiserum and centrifuging out the resulting specifically-formed precipitate.

The investigators suggest that a strong negative charge on the antibodies partly accounts for their contrasensitizing activities. To test this speculation, they treated antisera known to contain antibodies but devoid of contrasensitizing activity by a process called carbamylation which makes the antibodies more negatively charged than they are in the unaltered state. The treated antisera acquire the ability to suppress induction of delayed hypersensitivity in mice.

The researchers concluded that a subclass of $7S\gamma_1$ serum antibodies with strong negative charge are primarily responsible for controlling induction of delayed hypersensitivity to purified proteins in mice, and that this negative charge is itself important in their function. They also suggested a simple

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chemical method for transforming noncontrasensitizing antibodies into antibodies which can suppress sensitization.

Alfred J. Crowle, Ph.D, principle investigator, presented a report of the research at the annual meeting of the Federation of American Societies for Experimental Biology in April, 1975.

The study was supported by the National Institute of Allergy and Infectious Diseases.

#

PSORIASIS--Nearly eight million Americans have the reddish patches of skin called psoriasis. Psoriasis is hereditary and only one parent need be affected for a child to develop psoriasis, according to the National Institutes of Health.

RETINAL DETACHMENT--Retinal detachment is a separation of the inner from the outer layer of the retina, the light-sensitive tissue at the back of the eye. The National Institutes of Health reports that this condition, which can cause permanently impaired vision, occurs most commonly in men, the very nearsighted, and the aged.

METABOLISM--Metabolism is the amazing process whereby the body biochemically transforms food into tissue elements and into energy for growth, repair, and general body functions, according to the National Institutes of Health.

#

Research Advances

ROLE OF GLUCAGON STUDIED IN DIABETIC KETOACIDOSIS

Scientists conducting research funded by the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) have found that juvenile diabetics develop hyperglucagonemia in response to acute insulin deprivation. This finding suggests that glucagon may play an important role in the development of diabetic ketoacidosis.

John E. Gerich, M.D., and associates of the University of California, San Francisco, reported their findings in the *Journal of Clinical Endocrinology and Metabolism*, March 1975.

Diabetic ketoacidosis is a grave metabolic state of imbalance, associated with poor diabetes control, that requires emergency therapy. Two years ago, a NIAMDD grantee showed that plasma glucagon levels are elevated in human diabetic ketoacidosis, and are correlated with the severity of the ketoacidosis. It has not been known, however, whether increased plasma glucagon levels precede or result from the ketoacidosis.

Dr. Gerich found that plasma glucagon levels rise abruptly in insulin-dependent juvenile diabetics maintained solely on intravenous regular insulin infusions. These samples were compared with blood specimens obtained from the same subjects at one- to two-hour intervals for ten hours after insulin infusions were terminated.

Within one hour after discontinuing insulin infusion, plasma glucose, beta-hydroxybutyrate, and glucagon levels rose significantly. Within ten hours, all of these factors reached levels found in spontaneous diabetic ketoacidosis. Plasma free fatty acid and glycerol levels rose as expected after insulin

(more)

GLUCAGON (Cont'd)

deprivation, while plasma growth hormone and cortisol levels were not affected. Because increased plasma glucagon levels preceded increased plasma alanine levels, it is unlikely that alanine, a known stimulant of glucagon secretion, initiated the observed hyperglucagonemia.

#

INFECTIOUS DIARRHEA--Gastrointestinal disease (or intestinal flu) causes misery to whole communities of persons. National Institute of Allergy and Infectious Diseases scientists have recently identified a small virus, called the Norwalk agent, as a common cause of many of these outbreaks. Infant diarrhea, which causes many deaths around the world, is related to yet another virus. Work is in progress which scientists hope will one day lead to effective vaccines or other means of protecting people from these world-wide infections.

WILMS' TUMOR--In a study conducted by the National Wilms' Tumor Study Group, one of the National Cancer Institute's cooperative clinical groups, a combination of surgery, radiotherapy, and chemotherapy effectively treated Wilms' tumor, a childhood cancer of the kidney. The investigators reported a two-year survival rate of approximately 80 percent of 196 patients treated with surgery, radiation, and the anticancer drugs actinomycin D and vincristine.

#

Photo Feature

GROWTH HORMONE INJECTION SOLVES A TYPE OF DWARFISM

Children who grow slowly due to a hormone deficiency have a condition called hypopituitarism. The key to treating this disorder is human growth hormone (HGH), an extract of the pituitary gland.

Dwarfism, defined as an adult height of less than five feet, can have many causes, including thyroid problems, delayed adolescence, and genetic factors. Only hypopituitarism, however, responds to HGH therapy.

HGH is one of ten hormones produced by the pituitary gland, an organ a little larger than a pea that lies beneath the brain at the base of the skull. Released into the blood, HGH increases the level of sugar in the blood for energy, and helps accumulate amino acids, necessary for building proteins.

Treatment with HGH may be indicated for a child who is short, whose growth is less than 1-1/2 inches per year, and who has delayed dental eruption and bone age. The physician makes a diagnosis based on family history for stature, the child's growth rate, physical examination, and X-rays to determine bone age. A blood test for thyroid and pituitary hormone levels may also be carried out.

Some experts estimate that more than 10,000 children in the United States are severely stunted by hypopituitarism. Only about 750 of these children in any given year are presently being treated. The main reason for this is a severe shortage of HGH for therapy. The HGH extracted from a pituitary gland at autopsy is only enough for treatment of one individual for three or four days. At least 120 pituitaries per year are needed for one child.

To get more hormone for children with hypopituitarism, the National Pituitary Agency (NPA) was created in 1963 by the National Institute of

(more)

Arthritis, Metabolism, and Digestive Diseases. Using human pituitary glands obtained from voluntary donors after their death, NPA began collection on a national scale. Although the NPA now obtains five times the number of human pituitary glands available in 1962, supplies are still not sufficient to treat all children with hypopituitary dwarfism.

HGH shortages will be ended if researchers learn how to synthesize this hormone. HGH was chemically produced for the first time in 1971, but some errors in the formula rendered the product less than fully effective. Scientists are attempting precise HGH duplication. HGH synthesis will aid not only hypopituitary dwarfs and patients with other disorders, but will also further investigations of physiology.

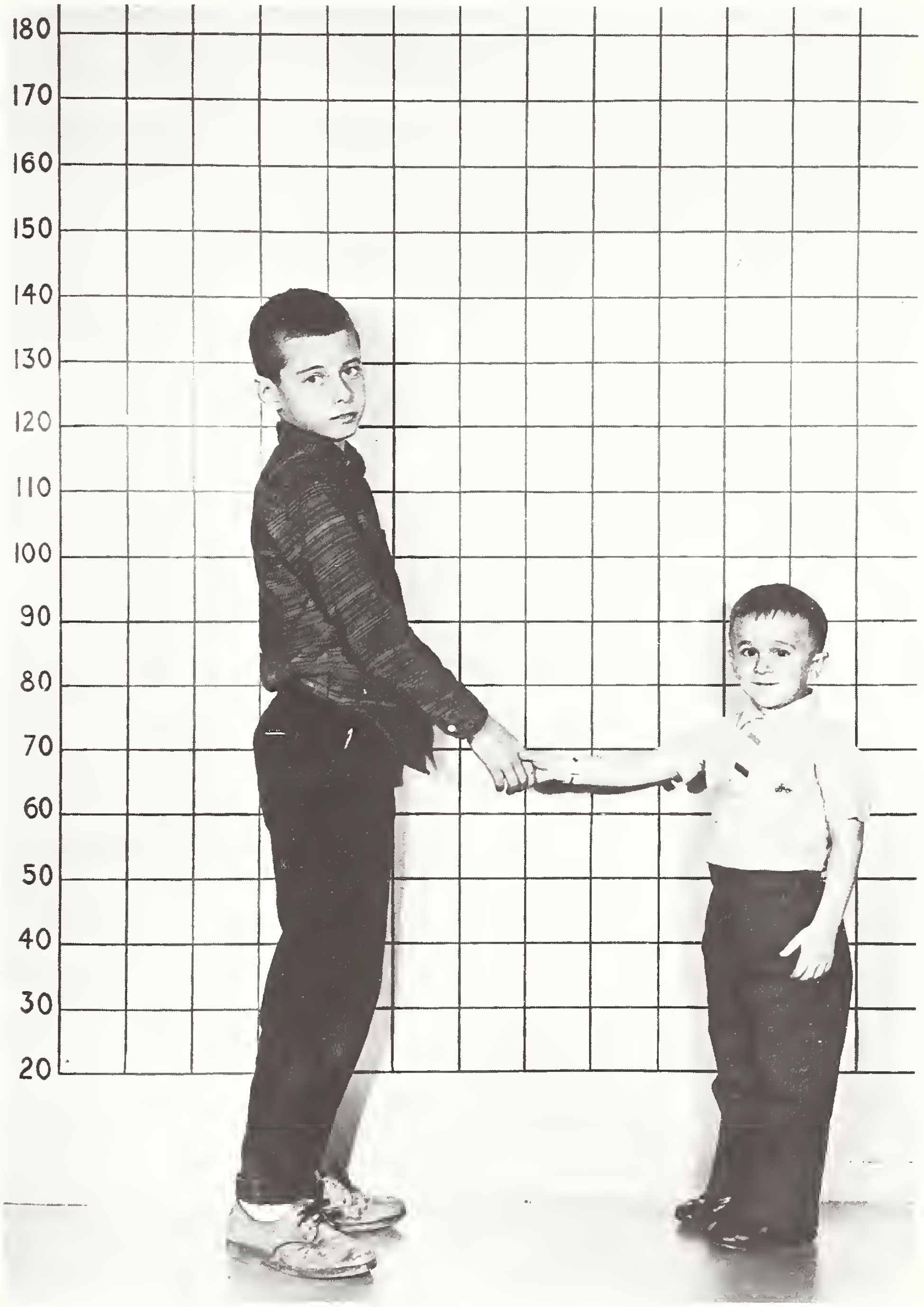
The NPA, which is located in Baltimore, Maryland, is directed by Salvatore Raiti, M.D. Dr. Raiti is an associate professor and director of pediatric endocrinology at the University of Maryland School of Medicine. He received his medical degrees at the University of Queensland, Australia, and trained in pediatrics in Australia; Edinburgh, Scotland; London, England; and in the United States.

(more)

Dr. Raiti is accurately measuring the height of a hypopituitary dwarf. The patient is standing straight against a wall on which a metal tape has been fixed. A metal right angle is placed on the top of the head.(NIH Photo #1410)

(more)

HORMONE (Cont'd)



Both patients were 12 years old when this photograph was taken. The hypopituitary patient (right) is the average height of a three-year-old boy. After many years of HGH therapy, the patient is now over five feet tall. (NIH Photo #1411)

#

News Feature

NINCDS Announces ...

COMPREHENSIVE EPILEPSY PROGRAMS TO BE STARTED

Comprehensive epilepsy programs sponsored by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) were formally initiated June 30, 1975, when representatives from Good Samaritan Hospital and Medical Center in Portland, Oregon; the University of Virginia Medical Center, Charlottesville; and the University of Minnesota Health Sciences Center, Minneapolis; signed contracts establishing comprehensive programs at their institutions.

The goals of the comprehensive programs are to facilitate clinical research and to coordinate research and teaching with health care services related to persons with all types of epileptic seizures within a defined geographic area. A primary objective of the programs is to assure the application of research findings to patients as early as possible. The programs will also assist clinical research by identifying those patients who are most in need of new techniques.

Funds for these centers will be directed toward research, coordination of health services in the area, and improvement of services by eliminating duplication and by identifying gaps in services. Direct payment for health services is not intended with these programs. There will be close affiliations with other Federal, state, and local agencies. Local chapters of the Epilepsy Foundation of America are expected to play a role in the community phase of the programs.

The NINCDS Applied Neurological Research Branch will sponsor the epilepsy centers, with J. Kiffin Penry, M.D., branch chief, serving as project officer.

(more)

EPILEPSY (cont'd)

James Cereghino, M.D., and Lawrence Smith will be co-project officers.

The programs have a five-year projection, but funding for these centers will be for one-year periods, since contracts are based on Congressional approval and appropriations. In the coming fiscal year, the University of Minnesota will receive $878,062; Good Samaritan Hospital, $990,131; and the University of Virginia, $499,794. Additional contract awards are contemplated for the next fiscal year.

Congress has expressed particular interest in this concept and Donald B. Tower, M.D., director of NINCDS, has pointed out the importance of the project not only for epilepsy, but for use as a model for other neurological and communicative disorders.

Principal investigators at the Centers are Fritz E. Dreifuss, M.D., professor and vice chairman, Department of Neurology at the University of Virginia; James Schimschock, M.D., director, Good Samaritan Child Neurology Clinic; and Robert J. Gumnit, M.D., head of the Neurology Department, St. Paul-Ramsay Hospital.

Much of NINCDS's development of these projects has been the direct result of the National Institutes of Health's Epilepsy Advisory Committee recommendations.

#

NORMAL VOLUNTEERS--By studying healthy volunteers at the National Institutes of Health Clinical Center, scientists gain insights into body functions in disease. The normal volunteers are often from church groups, civic organizations, and student groups.

#

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News Feature

Animal Studies...

POSSIBLE ROLE OF MUSCLE FORCES IN MALOCCLUSION IS EXPLORED

Despite the widely-held belief that malocclusion is an inherited problem, a group of scientists at the University of California at San Francisco School of Dentistry are testing their hypothesis that several types of malocclusion are due to improper balance among various muscle forces.

With support from National Institute of Dental Research research grants, Egil P. Harvold, D.D.S., Ph.D., and his associates plan electromyographic studies of individual muscles that are used in respiration, chewing, swallowing, and opening and closing the mouth.

His group will also study the effects in animals of shortening some muscles to increase tension, and of releasing ligaments to reduce tension in order to determine whether changing the muscle forces on bone could help people overcome disfiguring or incapacitating problems of malocclusion.

It is hoped that this project will contribute information about the causes of abnormal development of the jaws and face, and about how early intervention during active growth periods can be used to promote normal development.

Dr. Harvold also is studying an appliance called the Andresen activator which is used to help patients whose lower jaws are underdeveloped. He has found that this appliance can, in certain cases, direct the forces of specific muscles to enhance the growth of the facial bones and erupting teeth, and gradually bring them into more harmonious relations with the rest

(more)

of the mouth. This procedure requires no surgery or orthodontic bands. However, it is still necessary to learn which types of malocclusions respond to this treatment, and whether the adjustments produced by the activator are stable after patients stop using the appliance.

#

ARTERY HARDENING--Every artery throughout the body is subject to hardening, but the most often and most seriously affected vessels are the largest arteries, such as the aorta; the coronary arteries, and the arteries that feed the brain and kidneys. Arteries may harden in one part of the body more rapidly than in other areas, according to the National Institutes of Health.

CARDIOVASCULAR SYSTEM--The body's circulatory system--also called the cardiovascular system--is made up of the heart and the arteries, capillaries, and veins. The heart contracts about 70 times each minute, pumping oxygen- and food-rich blood into all regions of the body to nourish the muscles and tissues, according to the National Institutes of Health.

EARLY START--Hardening of the arteries may actually begin in early youth, perhaps even at birth. How troublesome it eventually becomes varies with each individual who has it. Some escape any consequence of the condition whatsoever. Others develop some symptoms, but with proper medical care continue normal and productive lives, according to the National Institutes of Health.

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NEWS & FEATURES From NIH July 10, 1975

Photo Feature

"MINI-SOCIETY" OF MONKEYS STUDIED IN NATURAL SETTING

A study which may result in improved birth control methods in humans is being conducted in Beaverton, Oregon, with a miniature society of 150 monkeys.

The monkeys, a group of Japanese macaques, live naturally in a two-acre enclosure at the Oregon Regional Primate Research Center, which is supported by the Division of Research Resources. Studies of behavioral reproductive biology, including experimentation with implanted intrauterine contraceptive devices (IUD's), are conducted on the monkey colony to increase understanding of sexual behavior of the female nonhuman primate.

"We are interested in determining whether an IUD will affect a female's behavior," says G. Gray Eaton, Ph.D., head of the Japanese macaque studies. "We also plan to explore whether and how the timing of sexual behavior is coordinated in males and females."

The original troop of 49 wild monkeys roamed the outskirts of Mihara, Japan. When its devastation of farm crops became too great, the troop was captured in 1965 and offered to the Oregon center. The group has thrived and now numbers 150 animals.

In addition to the IUD studies, the Japanese macaque compound is now a national observation center for social behavior studies by primatologists and psychologists. The scientists have observed the monkeys' play patterns, dominance relationships, and grooming and eating habits. Scientists are also investigating parental behavior, sexual behavior, and aggression in this monkey group, which is unique and very valuable scientifically due to the natural selection of its members in the wild.

(more)

Observers have found that monkey troops have two types of social rank: basic and dependent. Basic rank is fought for by the monkey, who is ranked by the outcome of aggressive acts with its fellows. Dependent rank is gained through alliance with high-ranking monkeys, especially mothers and dominant males. Female Japanese macaques have a close and long-lasting relationship with their offspring. A high-ranking mother, therefore, will have high-ranking offspring.

"Many questions about the evolution and development of primate behavior remain unanswered," said Dr. Eaton. "Preliminary data suggest that there is an 'incest taboo' in the troop. Among animals born here at the Center, no brother-sister or mother-son matings have been observed."

Sexual and aggressive behavior among the monkeys fluctuates seasonally, said Dr. Eaton.

"Males attack each other ferociously during the fall breeding season," he said. "Then they play together like infants during the summer. Presumably, differences in hormone levels interact with brain nerve mechanisms to induce these seasonal differences. The causes of fluctuating hormone levels and their interaction with cerebral neurons are current subjects of investigation."

The Japanese macaques roam freely in their enclosure, bounded by an 11-foot fence. Observers sit in towers along the fence and tape record the monkeys' behavior. Noteworthy events are keypunched and analyzed with the Center's computer.

(more)

"MINI-SOCIETY" (Cont'd)

A male Japanese macaque monkey surveys the surroundings from his precarious perch at the Oregon Regional Primate Research Center, Beaverton. Sex and reproductive studies are major projects being conducted with monkeys living on the two-acre complex. The Center is supported by the Division of Research Resources. (NIH Photo #1412)

#

News Feature

INTERNAL MEDICAL DIAGNOSIS HELPED BY ULTRASONIC WAVES

Biomedical engineers in the Division of Research Services (DRS) aid research in several ways. One effort is directed against the difficult problem of medical diagnosis when inspection of the inner organs is restricted. X-ray photographs can provide pictures of internal skeletal structures and, to some degree, outlines of organs. X-ray methods, however, do not clearly detect the boundaries of softer tissues such as muscles, brain, and tumors. It must be used sparingly, since excessive exposure to radiation adversely affects living organisms.

Engineers and physicians working together have been searching for a safe, external method to display body structures pictorially. Remarkable success has been achieved by exploiting acoustic energy (sound) as used in sonar systems to detect and track solid objects under the sea. One form of acoustic scanning, called echo-sonography, transmits high frequency waves into a sound-conducting medium and measures the time required for signals to reach and echo back from the reflecting surface. Given the direction of the transmitted beams and the acoustic velocity of the medium traversed, one can record depth and dimensions.

Ultra-high frequency sound waves directed into the body echo with different intensities from various tissues. Sound waves at frequencies much higher than those audible to the human ear are required; typical frequencies for medical use range from one to ten million cycles per second. The upper limit for human hearing is approximately 20,000 cycles per second.

Ultrasonic waves produce images similar to those of X-rays. Signals pass through the body, with hard structures conducting sound energy to a greater extent than soft tissues. The sound waves provide diagnostic information other-

(more)

wise unobtainable. They can distinguish many different kinds of tissue, examine a fetus inside a mother's body with no harm to either, and detect tumors, lesions in the eye, gallstones, benign cysts, and kidney and liver abnormalities.

A team of specialists from DRS, the National Heart and Lung Institute, and the National Aeronautics and Space Administration developed and improved an ultrasonic system for non-invasive visualization of heart structure to evaluate effects of prolonged weightlessness on astronauts, by recording dimensions of astronauts' heart muscles just prior to lift-off, and immediately after splashdown, during the Skylab III flight.

#

CANCER CLASSIFICATION--Cancer is classified into two major categories: solid tumors which build up in the lungs, brain, breast and other major organs, and hematological malignancies, which arise from the blood and lymph systems. Physicians treat solid tumors with modes of localized therapy if the condition is diagnosed early. They can remove the tumor by surgery or destroy it with radiation. Hematological malignancies are usually spread throughout the body at the time of diagnosis. Chemotherapy with anticancer drugs, sometimes in combination with other therapy methods, offers possible treatment, according to the National Institutes of Health.

#

Research Illustrated

NATIONAL LIBRARY OF MEDICINE SEARCHES JOURNALS FOR DATA

The National Library of Medicine produces Index Medicus *and individual on-line bibliographies through its Medical Literature Analysis and Retrieval System (MEDLARS-MEDLINE). Journals included in the* Index Medicus *are received and recorded in the Division of Technical Services before being sent to literature analysts for indexing.(NIH Photo #1413)*

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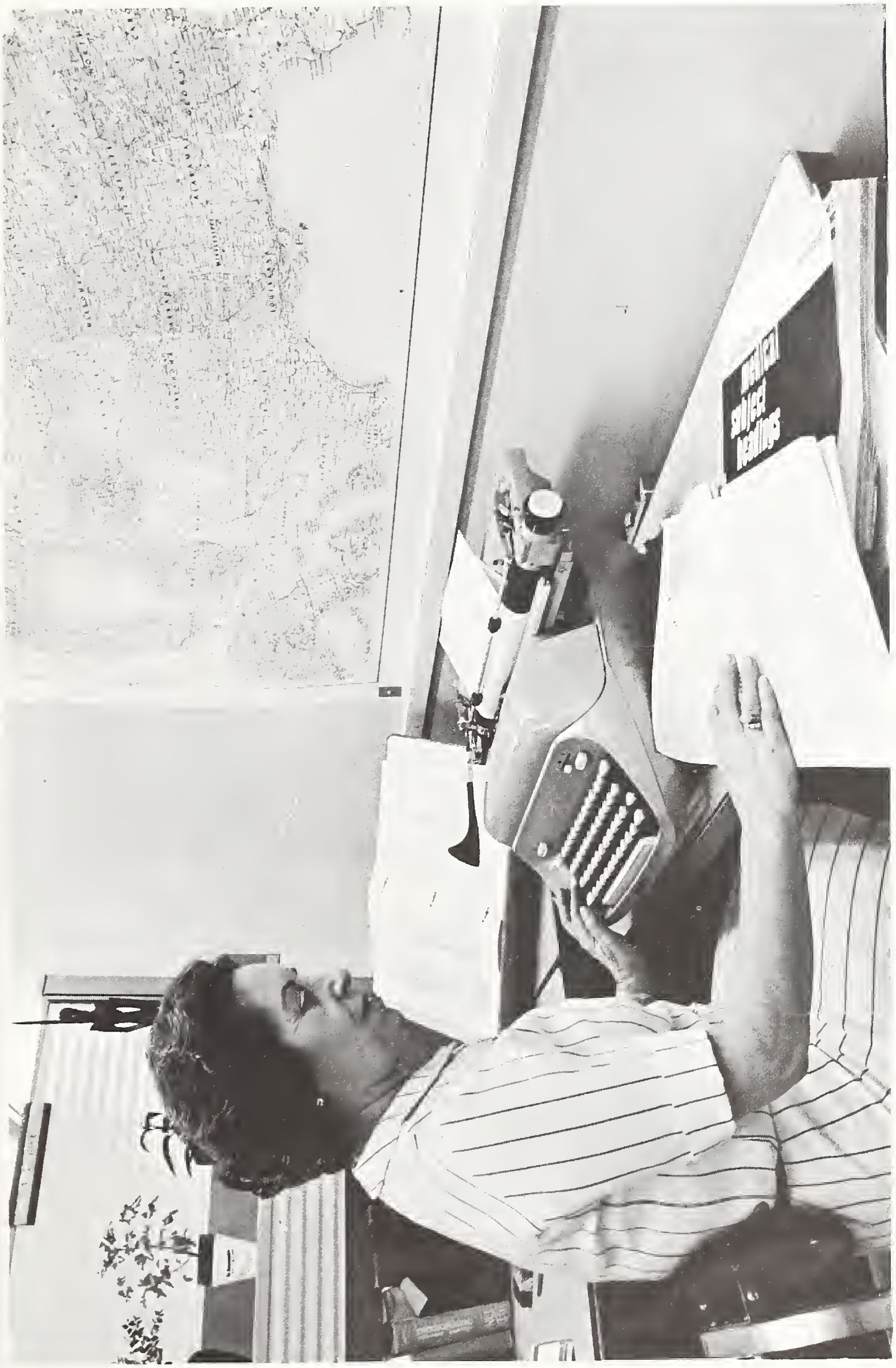

About 3000 different medical journals are indexed for Index Medicus. *Literature analysts read each article of a journal, assigning medical subject headings and subheadings for every major theme in the article. Ten or 12 subject headings may be used to describe an article. Bibliographic information and the medical subject headings are typed onto a data form and then entered into the computer for processing and storage.* (NIH Photo #1414)

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JOURNALS (Cont'd)

From the literature analysts, Index Medicus *journals with their data forms go to Input for encoding onto magnetic tape using Keymatic Encoders. Each article record contains bibliographic data and medical subject headings that describe the article. These records are stored on magnetic tape or disc pack for later retrieval.(NIH Photo #1415)*

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JOURNALS (Cont'd)

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NEWS & FEATURES From NIH July 10, 1975

Disease Profile

SCLERODERMA IS A RARE RHEUMATIC DISORDER OF CONNECTIVE TISSUES

Scleroderma, or progressive systemic sclerosis, is a relatively uncommon member of the family of rheumatic diseases. It is a generalized disorder of the connective tissues which affects the skin, joint coverings, and internal organs such as the esophagus, intestinal tract, heart, lungs, and kidneys. Though scleroderma can develop in any age group, it is more commonly found in persons between the ages of 25 and 55, and affects women two to three times more often than men.

The disorder may be divided into two general categories: localized and systemic. One type of localized scleroderma, morphea, takes the form of waxy, drop-like patches on the skin. It may occur at any age and at any body site, and remains confined to the skin.

Linear scleroderma, usually developing in childhood, is characterized by a streak or band of hardened, waxy skin on the arm, leg, or forehead. This form of the disorder extends deeper into the tissue and muscles, and may interfere with the motion of the affected joint (usually fingers, elbows, or knees), possibly requiring surgical correction.

The more generalized type of scleroderma, progressive systemic sclerosis, affects not only the skin and underlying tissues, but also the internal organs. The connective tissue becomes hardened and fibrous, often resulting in a loss of joint flexibility as well as difficulties in the normal function of the affected organs.

Numbing and discoloration of the fingers (Raynaud's phenomenon), swelling

(more)

or stiffness in the extremities, and gradual thickening of skin on the hands may signal the onset of scleroderma. From the initial site, the condition may spread to other parts of the body. As scleroderma progresses, the skin becomes taut and shiny, leading to a loss of normal skin folds and a mask-like facial expression. Infection and ulceration of fingertips are not uncommon, and shortening of the digits may occur, particularly among patients with Raynaud's phenomenon. Joint immobilization often results from contractures of muscles and tendons, and tight encasement in thickened skin.

The course of the disease varies among patients. In some, the condition may stabilize, and may even show signs of regression. Other patients evidence only external symptoms of scleroderma with slow, progressive loss of hand function. Still others show few external symptoms, but develop rapid involvement of internal organs.

Generally, the outlook is significantly poorer when there is clinical evidence of involvement of vital organs such as the kidney, heart, or lung at the time of diagnosis.

Malfunction of the esophagus, often the first indication of internal complications, occurs in many patients. Beginning with mild discomfort during or after eating, it may later present difficulty in swallowing solid foods. Of the internal organ systems, the gastrointestinal tract is most often involved in the progression of scleroderma. More than half of all patients experience swallowing difficulties, heartburn, nausea, and related gastrointestinal problems as a result of their disease. Vomiting, abdominal pain, and diarrhea may also signal small bowel involvement.

(more)

Difficult, labored breathing after exertion is the most common cardiorespiratory complication and is present in more than 50 percent of scleroderma patients. Although fibrous tissue gradually replaces the normal tissues of the lung and heart muscle, patients may not exhibit symptoms if their physical activity is restricted. The most frequent causes of death are cardiopulmonary insufficiency and kidney failure. In cases of less severe visceral (internal organ) dysfunction, however, slowly progressive scleroderma is not necessarily fatal.

The cause of scleroderma is as yet unknown. Although no current method of treatment is of consistent value, physicians do employ various forms of physical and drug therapy to ameliorate the thickening and hardening of connective tissues throughout the body.

X-rays play an important role in diagnosis and evaluation of progressive disease. This technique provides the physician an accurate view of the extent of fibrous tissue growth in various body sites such as the chest and hands. Barium tests of the upper and lower gastrointestinal tract, electrocardiograms, and pulmonary function tests all aid the physician in assessing the severity of the disorder.

Various supportive measures are useful in compensating for damage to skin, joints, and internal organs. Avoiding exposure to cold and the use of special creams, soaps, and bath oils help to protect the hands and relieve excessive dryness of skin. Medications are also available to alleviate pain and infected fingertip ulcerations. If swallowing becomes difficult, foods that are easily ingested, in conjunction with antacid therapy, may lessen eating discomfort.

(more)

SCLERODERMA (cont'd)

A number of drug agents have been employed in an effort to inhibit the underlying processes that result in progressive fibrosis of the connective tissue. Because so little is known of these processes, however, treatment with various agents has met with little success. Small doses of anti-inflammatory drugs (corticosteroids) have been of some temporary benefit in the acute stages of the disease; however, these agents have proven ineffective in retarding the progression of scleroderma. Evaluation of treatment is made more difficult by the slow nature of the disease and by the possibility of spontaneous improvement or remission.

Studies are currently underway in medical centers around the country to increase our basic knowledge of scleroderma. High among the research priorities is the pinpointing of the underlying mechanism in the development of excessive fibrous tissue throughout the body. Once the cause of this process has been determined, the search for effective methods of treatment will gain momentum. In the meantime, investigators continue to seek forms of therapy which will not only alleviate the symptoms of scleroderma, but will also retard its progression.

Scleroderma is one of the research interests of the National Institute of Arthritis, Metabolism, and Digestive Diseases.

#

CATARACT SURGERY--Cataract surgery is one of the most successful operations performed today. From 90 to 95 percent of patients undergoing this operation regain useful vision, reports the National Institutes of Health.

#

News Releases Issued

MINORITY SUPPORT--Two-year colleges, native American Indian tribes, and institutions with significant enrollment from ethnic minority groups are now eligible for research support under the NIH Minority Biomedical Support Program.

The regulations, published in the June 30, 1975, *Federal Register*, broaden eligibility for the Program, which is designed to encourage greater participation by minority group members in biomedical research. Under the original provisions of the Program, grants were awarded for this purpose to predominantly minority colleges.

When the Program was started in 1972, only four-year academic institutions with a student enrollment of at least 50 percent from ethnic minority groups were eligible for grants. The Program, administered by NIH's Division of Research Resources, now funds 69 grants involving 75 such institutions.

In addition to four-year colleges with 50 percent or more minority student enrollment, eligibility will now be extended to include two-year colleges with a traditionally high (more than 50 percent) minority student enrollment; institutions with a significant student enrollment (but not necessarily more than 50 percent) which is derived from ethnic minorities; and an Indian tribe which has a recognized governing body and which performs substantial governmental functions, or an Alaska Regional Corporation as defined in the Alaska Native Claims Settlement Act.

#

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NEWS & FEATURES From NIH July 25, 1975

Research Advances

New Vitamin C Study ...

ASCORBIC ACID INHIBITS RHINOVIRUS REPLICATION

Prepared by Ms. Jeannette Belliveau

A husband and wife research team has found that ascorbic acid significantly inhibits rhinovirus replication in human diploid cells. This experiment was designed to help determine if Vitamin C treatment, at the cellular level, might be effective in preventing or alleviating common cold symptoms.

This research work was supported in part by a training grant from the National Institute of Allergy and Infectious Diseases. The work was reported in the April, 1975 issue of *Proceedings of the Society for Experimental Biology and Medicine*.

Patricia R. Schwerdt and Carlton E. Schwerdt, Ph.D., biochemists at the Stanford University School of Medicine, exposed human cell cultures to ascorbic acid (Vitamin C) for two days. They then infected the cultures with rhinovirus serotype 20 (RV-20), one of many viruses that cause the common cold. The ascorbic acid treatment, continued during virus replication, did not affect initial growth of the virus, but thereafter it suppressed virus replication, until yields of ascorbic acid-treated virus after 48 hours were 1/40 of control yields.

The reason for this suppression of growth is not certain. One of the initial growth experiments produced some evidence that an activity similar to that of interferon, an infection-fighting protein produced by human cells, hampered virus growth.

The scientists chose the cellular level of inquiry to control several variables beyond the reach of an investigator working with human subjects. The

(more)

experimental design included control of factors such as the concentration of ascorbic acid and its toxicity for human diploid cells; the thermal inactivation of rhinovirus in the presence of ascorbic acid; and the multiplicity of infection.

Preliminary research showed that an ascorbic acid concentration of 250 mcg/ml plus glutathione had no adverse effect on uninfected, confluent WI-38 human cells. Glutathione, a chemical isolated from yeast, was added to prevent oxygenation of the ascorbic acid. This concentration was then used in the experiments.

The scientists found that during the first 16 hours post-infection, the presence of either ascorbic acid or glutathione alone did not affect the growth of RV-20. However, in the presence of the ascorbic acid-glutathione mixture, the virus yield dropped gradually during the period of 16 to 48 hours post-infection, reaching only 1/20 of the control yield at 32 hours, and 1/40 of the control yield at 48 hours. The presence of both reagents also delayed initial virus replication.

Assay of culture samples for interferon revealed that in one initial growth experiment, an interferon-like activity was present at low levels 5 to 17 hours post-infection in samples treated with the ascorbic acid-glutathione mixture.

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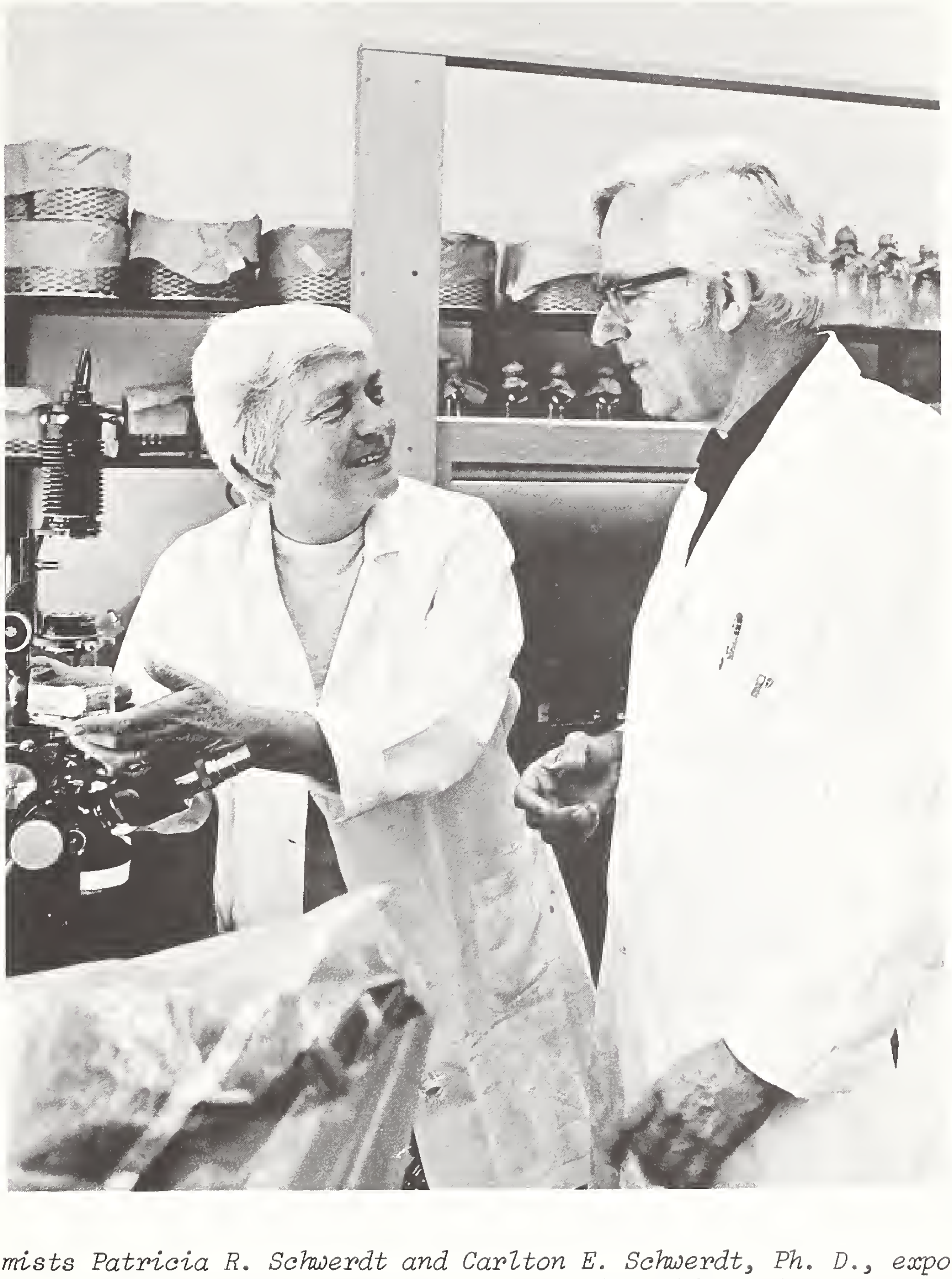
ASCORBIC ACID (Cont'd)



Biochemists Patricia R. Schwerdt and Carlton E. Schwerdt, Ph. D., exposed rhinovirus grown in their laboratory to ascorbic acid specially treated to prevent oxidation. They found that virus replication was severely hampered by the ascorbic acid, perhaps due to an interferon-like activity. The Stanford University scientists were trying to determine if Vitamin C, at the cellular level, might lessen common cold symptoms. (NIH Photo #1417)

#

Research Advances

SEXUAL SKIN COLORATION AIDS IN BREEDING SOME MONKEYS

Coloration of the sexual skin of female rhesus monkeys can be used as a reliable indicator to identify peak intervals for conception, Wisconsin Primate Research Center investigators have determined.

A three-year project on the use of coloration of the sexual skin (tissue around the female perineum) as a guide for timing mating and artificial insemination has been completed. The results of the studies at the Madison Center, supported by the NIH Division of Research Resources, identify a new technique for maximizing breeding success in primates.

In one study, 109 female rhesus monkeys were artificially inseminated once during a given menstrual cycle, at a time when sexual skin was a relatively intense red. The procedure produced a 48.2 percent rate of successful impregnation. This is a higher rate than previously reported in studies using single inseminations (natural or artificial) in which the time of ovulation was estimated by calendar methods. (The calendar method of breeding has been a standard whereby a day between the 11th and 14th day of the menstrual cycle is considered the best time to mate the animal or artificially inseminate her.)

The research team, Dr. John A. Czaja, Dr. Robert W. Goy, and breeding colony supervisor Stephen G. Eisele, contend that the calendar method is relatively inefficient because primate menstrual cycles can vary widely in length and may continue to occur in the absence of ovulation.

The usefulness of skin coloration (which ranges from virtually white

(more)

to a very deep red) stems from the fact that rhesus color level appears to reflect levels of certain female sex hormones (estrogens) produced by the ovary. Primates are now known to consistently show a distinct increase in these estrogens shortly before ovulation.

Determining the day of ovulation or conception is important for many aspects of research on primate reproduction. Observations of sex skin coloration, according to Dr. John A. Czaja, provide a ready guide to ovarian condition and an easy visual indicator of the period of maximum fertility.

"Tracking ovarian condition and detecting ovulation has been a continuing problem in the rhesus monkey," Dr. Czaja said. "Although there are increasingly sophisticated and successful techniques in the laboratory that can aid in this effort, most are either expensive or require expertise in physical examination. This tends to rule out their use in many laboratory breeding programs. Our method simplifies the process with good results."

Based upon an analysis of sex skin color change around the day of conception, the researchers report: "Inseminations most successful in producing pregnancies occurred two to four days prior to color breakdown (rapid and consistent decline or fading from peak sex skin color). This correlation suggests a strong relationship between skin color and sex hormone change. Average peak color and incidence of color breakdown occurred after the time of successful insemination, and are therefore most useful in retrospective analyses. Knowing the day of color breakdown allows one to more closely estimate the period of maximum fertility and, within days of insemination, predict the probability that an insemination would prove

(more)

successful."

Detailed findings of this female rhesus monkey reproductive study were presented in the July 1975 issue of *Federation Proceedings*, published by the Federation of American Societies of Experimental Biology.

#

MALIGNANT MELANOMA--Investigators supported by the National Cancer Institute report that patients with advanced malignant melanoma, a form of skin cancer, can be helped with use of immunotherapy in combination with other modes of cancer therapy. Research physicians treated melanoma patients with DTIC, an anticancer drug, and BCG, a bacterial preparation that stimulates the immune defense system. The combination of the treatments produced a partial response in 27 percent of an 89 patient group. In 20 patients in which the disease spread only to the lymph nodes, 55 percent responded to DTIC and BCG. The two therapies also improved the duration of responses and survival.

#

Research Advances

ATYPICAL DIABETES CASE IS LINKED WITH PANCREATIC TUMOR

David M. Kipnis, M.D., and Marie H. Greider, M.D., of Washington University, St. Louis, grantees of the National Institute of Arthritis, Metabolism, and Digestive Diseases, have described a case of uncontrolled diabetes, not typical of the juvenile or adult-onset form. Apparently the disease resulted from hyperglucagonemia associated with a glucagon-secreting islet cell carcinoma.

Evidence has accumulated in recent years to indicate that diabetes is characterized by excessive glucagon secretion, in addition to insulin deficiency, and thus may be a bihormonal disorder. The present case report, of a rare "experiment of nature," seems to support this hypothesis. The case concerns a woman with uncontrolled diabetes and hyperglucagonemia associated with a glucagon-secreting tumor of the pancreas. Drs. Kipnis, Greider, and associates reported their findings in *The American Journal of Medicine*, March 1975.

The 53-year-old patient had been hospitalized for regulation of her diabetes. Previously her condition had been well controlled with tolbutamide for nine years. She had no family history of diabetes and had had six normal pregnancies without evidence of gestational diabetes. She underwent a variety of metabolic studies and had a biopsy of an inoperable abdominal mass. The mass was diagnosed as an islet cell carcinoma, prior to her death seven months later.

A suspected diagnosis of hyperglucagonemia (600 to 1500 pg/ml plasma)

(more)

ATYPICAL DIABETES (Cont'd)

was confirmed by analysis of hourly blood samples for 24 hours, which also revealed a direct correlation between plasma glucose and glucagon. Paradoxically, oral glucose increased plasma glucagon levels whereas intravenous glucose decreased these levels. Arginine and epinephrine infusions also increased the plasma glucagon levels, but the latter stimulus was blocked by alpha adrenergic blockade.

Extensive study of the tumor in vivo (and at autopsy) revealed a growth pattern consistent with an origin from pancreatic islets. Glucagon content of the tumor was 0.78 micrograms/gram wet weight or 374 micrograms total glucagon. This increased concentration of glucagon in the tumor, compared to that of the plasma, indicates that the tumor was the source of the circulating glucagon.

The specific cause of this patient's diabetes is unknown. Although destruction of normal (insulin-secreting) pancreatic tissue by the tumor contributed to her disease, and a genotype for diabetes cannot be excluded definitively, it seems likely that her chronic, persistent hyperglucagonemia was a significant etiologic factor.

#

EMPHYSEMA--Life expectancy is reduced by circulatory complications combined with emphysema. Especially serious are such added problems as right-heart "overwork" owing to high blood pressure in the pulmonary blood vessels and an abnormal increase in the number of red blood cells, according to the National Institutes of Health.

#

TRACERS DETECT LENGTHY SURVIVAL OF TOXOPLASMA OOCYSTS IN SOIL

National Institute of Allergy and Infectious Diseases' grantees have used radioactive tracers to show that Toxoplasma oocysts in cat feces are still capable of causing toxoplasmosis after being buried in the soil for a year or more. The grantees, Drs. J.K. Frenkel, A. Ruiz, and M. Chinchilla of the University of Kansas Medical Center and the University of Costa Rica, reported their findings in the *American Journal of Tropical Medicine and Hygiene*, March, 1975.

Oocysts are the transmissible form of the parasite *Toxoplasma gondii*. Oocysts are excreted in the feces of infected cats and when dried they infect humans or domestic meat animals. The parasites are released within the human or animal body and produce the disease called toxoplasmosis. This disease is generally mild but can cause severe damage to an unborn baby if contracted by a pregnant mother.

One infected cat can excrete several million infectious oocysts. Dr. Frenkel and his colleagues evaluated the infective potential of these oocysts by determining their survival rates under varied soil conditions. The scientists fed radioactive strontium to infected cats and superficially buried the feces in several sites in Kansas and Costa Rica. After being in the soil for a year in Costa Rica and at least 18 months in Kansas, the oocysts were still infectious. Apparently they persist longer in moist areas.

Toxoplasma oocysts in the soil can be transmitted directly to humans, particularly to children playing in the dirt. Possibly this finding explains

(more)

the high incidence of toxoplasmosis in chidren under 5 years old in some areas of Central America.

Animals grazing or drinking in contaminated areas are susceptible to infection for as long as the oocysts survive in the soil. Eating the under-cooked meat of an infected animal is believed to be one way persons in this country acquire toxoplasmosis.

In the present study, flies that feed on contaminated feces were infectious as were their larvae. However, the hatched flies were not. Earthworms were markedly infectious. Further studies are being done to clarify the roles of these various transport hosts of *Toxoplasma gondii*.

#

CANCERS OF DIGESTIVE ORGANS--Cancers of the digestive organs account for one-fourth of new cancer cases in the U.S. each year and more than one-fourth of cancer deaths. Few patients with these cancers in advanced stages respond to treatment with single anticancer drugs, but by combining several drugs, 5-fluorouracil and those in the nitrosourea group, some studies show slight but significant increases in survival rates, according to the National Institutes of Health.

#

Research Advances

FREQUENCY OF ANTIGEN W27 IS INCREASED IN PSORIATIC ARTHRITIS

A grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases, Paul I. Terasaki, Ph. D. has shown that the frequency of the histocompatibility antigen, W27, is markedly increased in patients with psoriatic arthritis complicated by spondylitis, or inflammation of the vertebrae. The increased frequency of W27 is found in a number of other "rheumatoid variant" rheumatic diseases. Dr. Terasaki's finding suggests a common pathogenic mechanism among these disorders.

The remarkable relationship of the histocompatibility antigen W27 with ankylosing spondylitis, Reiter's syndrome, and the spondylitis associated with inflammatory bowel disease has been documented. This association has just recently been extended to include another "rheumatoid variant" disorder--psoriatic arthritis.

Dr. Terasaki of the University of California, Los Angeles, and his associates reported their findings in *Arthritis and Rheumatism*, April, 1975. They reported that the frequency of W27 is significantly increased in patients with psoriatic arthritis complicated by spondylitis, but not in patients with peripheral arthritis alone. The observations, coupled with the aforementioned findings, strongly suggest that some common pathogenic mechanisms are operative in all rheumatoid-variant diseases.

Forty patients with psoriatic arthritis and 254 normal control subjects were studied. Histocompatibility antigen (HL-A) typing was performed on each subject. The microdroplet lymphocyte cytotoxicity test was used to identify 26 different HL-A antigens.

(more)

PSORIATIC ARTHRITIS (Cont'd)

Radiographic spondylitis and/or sacroiliitis occurred in 23 of the 40 patients. W27 positivity was detected in 8 of these 23 patients (35 percent), in 3 of 17 patients (18 percent) with peripheral arthritis alone, and in six percent of the control subjects. W27-positive and W27-negative spondylitis were clinically and radiographically indistinguishable, except that W27-positive disease occurred exclusively in males with a shorter duration of psoriasis.

Thus, W27 positivity in males with psoriatic arthritis may enhance their risk of developing spondylitis. Further study of W27 frequency in the rheumatoid variant disorders should provide a better explanation of the interrelationships and familial aggregation which exist among these conditions.

#

OVARIAN CANCER--Ovarian cancer is the fifth leading cause of cancer deaths among American women. In some studies on patients with advanced ovarian cancer, a four-drug combination of cyclophosphamide, hexamethylmelamine, 5-fluorouracil and methotrexate produced an overall response rate of more than 70 percent, as compared with a 45 percent response with the standard single agent, L-PAM, according to the National Institutes of Health.

#

NEWS & FEATURES From NIH

July 25, 1975

Photo Feature

NEW CELL RECONSTRUCTION TECHNIQUE IS DEVELOPED

Prepared by Ms. Nancy Zimmerman

Sophisticated use of the biomedical million-volt electron microscope at the University of Colorado (CU), Boulder, has resulted in the perfection of a new technique in cell reconstruction. With the beam damage reduced and the penetrating power increased, the high voltage microscope obtains sharp 3-D images of the cell's structure. A clearly resolved view of whole intact cells at various subcellular components is now possible.

The work of the CU scientists at the Department of Molecular Cellular and Developmental Biology opens up many areas of research. Scientists are now able to mass produce millions of cells in different combinations of nuclei and cytoplasms. Expanding on previously developed methods, CU researchers can process a large number of "hybrid" cells composed of nuclei from one set of mammalian cells, and cytoplasms of another set. Drs. Keith R. Porter, George Veomett, David M. Prescott, and Jerry Shay comprised the research team which successfully developed the new cell reconstruction technique.

Using a special strain of mouse cells (L929), the CU scientists treat the cell with *cytochalasin B*. This compound is known to give a nucleus freedom to move to the outer edges of the cells. Then, only low centrifugal force is needed to pull the nucleus out of the cell, thus breaking the thin thread between nucleus and cytoplasm. The result is the formation of a karyoplast (a body containing the nucleus and a small amount of cytoplasm), and the cytoplast (a body containing the remainder of the cytoplasm).

The two processes, performed on different types of cells, provide

(more)

CELL RECONSTRUCTION (Cont'd)

scientists with karyoplasts from one set of mouse cells and cytoplasts from another set. When the karyoplasts and cytoplasts are exposed to an inactive virus, they re-fuse, and a mass of hybrid cells is produced.

To test the success of the fusion, a radioactive substance is fed to one group of cells in a culture, and tiny latex spheres (a plastic material similar to that added to latex paint) is fed to another set. The radioactive substance is known to be deposited in the nucleus, and the large latex spheres to be absorbed by the cytoplasm. When most of the resulting hybrid cells have both the radioactive materials and the latex spheres, CU scientists know that fusion is successful. The hybrid cells remain alive and continue to divide, thus proving that they are not impaired by the process. Laboratories throughout the United States have now adopted the new technique and are using it for their studies.

The high voltage electron microscope at CU is one of the only two existing million-volt electron microscopes in the country being used for biomedical research. The other one is located at the University of Wisconsin. Both are supported by the NIH Division of Research Resources.

Using the million-volt electron microscope in conjunction with a scanning microscope, the CU scientists are able to get 3-D views and pictures (micrographs) of the smallest particles in the cytoplasm and the nucleus. CU scientists are also studying the outside of the cell in minute detail.

Cancer cell research is a major project underway at CU. One study involves placing a nucleus from a "transformed" (cancer) cell inside the cytoplasm of a normal cell. Another study involves putting a normal nucleus

(more)

inside a cancer cytoplasm. Following such transplants, the relative influences of the nucleus and cytoplasm in cancer may be studied.

CU is also doing research in the area of muscular dystrophy. The Colorado scientists hope their new technique can provide some answers as to where the genetic breakdown has its primary effect--in the nerve cells, muscle cells, or both.

The million-volt electron microscope has enabled the researchers to intensively examine nerve dystrophy and muscle cells in mouse and chicken cultures. They have seen large molecules within the nerve-muscle membrane system never previously observed by researchers. Using the new technique, the scientists are attempting to combine normal nerve cell parts with dystrophic nerve cell parts, and normal muscle cell parts with dystrophic muscle cell parts.

The CU scientists point out that the field of molecular genetics grew from work primarily on *E. coli*, a one-celled bacteria found in human and animal intestines. With the new technique, prospects are improved for generating haploid cells (cells with only half the number of chromosomes in the body). CU scientists hope to combine the nuclei of mouse spermatids--haploid reproductive cells not as highly differentiated as sperm cells--with the cytoplasm of mouse cells, so they can better study the various genes which are involved in all types of cell phenomena.

The availability of the million-volt electron microscope is providing scientists with yet another valuable tool with which to solve the mysteries of cell formation and malformation.

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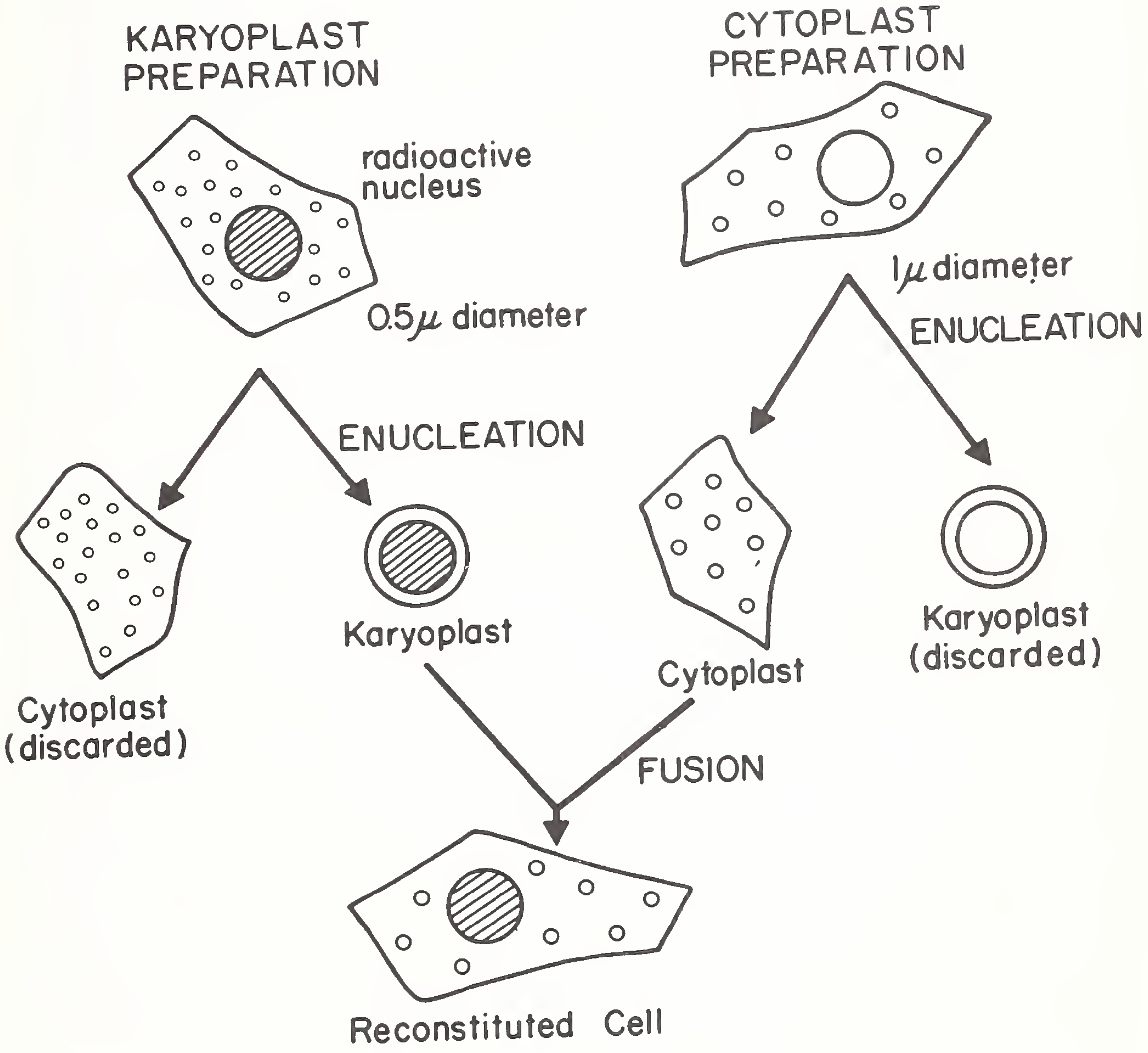
CELL RECONSTRUCTION (Cont'd)



This is a diagrammatic explanation of the reconstituted cell as evolved by University of Colorado scientists. The karyoplast preparation (left) provides the nucleus for the "hybrid" cell composite, treated with a radioactive substance. The cytoplast preparation (right) includes latex spheres absorbed by the cell's cytoplasm. The cells are then split by centrifugal force and the components allowed to recombine. The hybrid cell is identified by the radioactive nucleus and a cytoplasm with latex spheres. These hybrids continue to divide, indicating they are still alive and viable, and their function unimpaired.(NIH Photo #1418)

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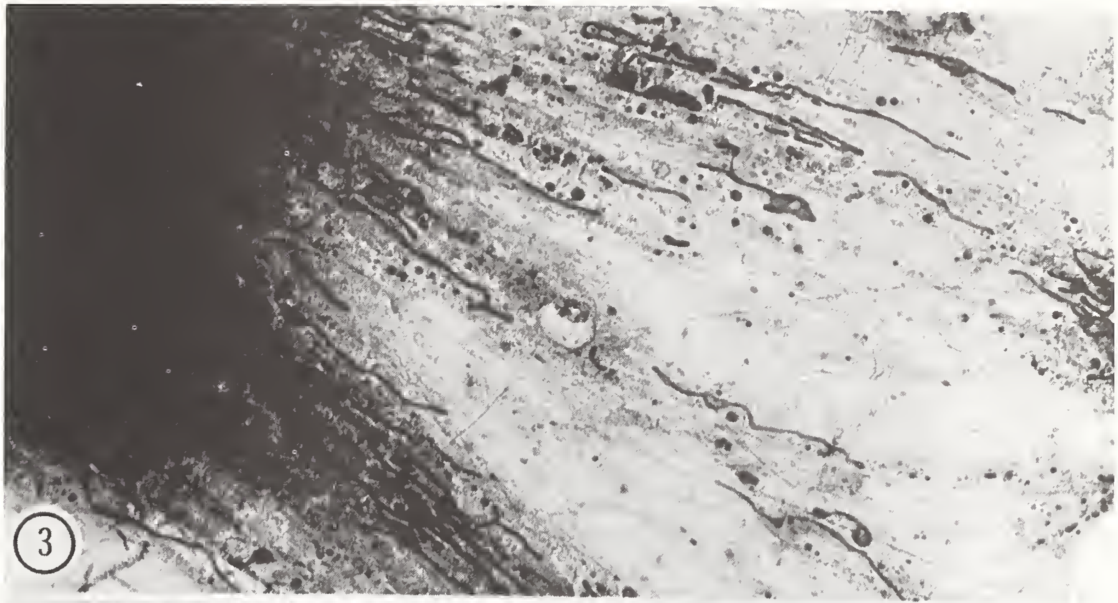
CELL RECONSTRUCTION (Cont'd)



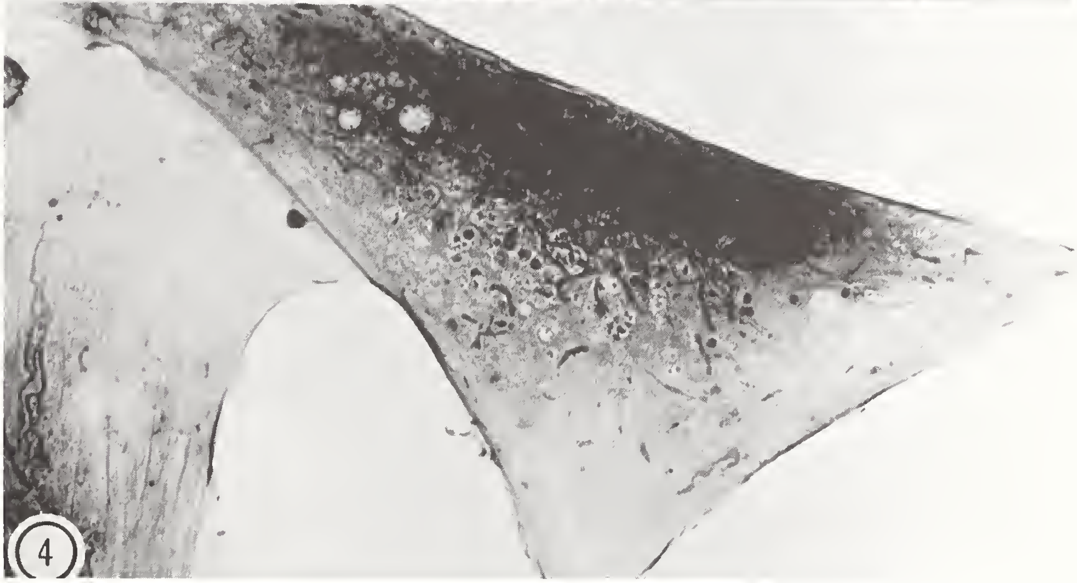


Figure 3 depicts a million volt electron micrograph of the thinner margins in a rat's whole muscle cell. The nucleus, not shown, is toward the upper left. Figure 4 is a micrograph of an enucleated muscle cell of a rat. Enucleation (removal of the nucleus) thins the cell which increases its visibility under the microscope. The dense area in the center most probably contains the centrioles and Golgi apparatus (centrosphere). The importance of the nucleus and cytoplasm in the control of muscle cell form and formation is being researched with the million-volt electron microscope.(NIH Photo #1419)

#

News Feature

EXTRA HEARTBEATS USUALLY NO CAUSE FOR ALARM

Extrasystoles, commonly called "palpitations" or "fluttering" by persons who have them, are simply extra or premature heartbeats. They are the most common of all the abnormalities of the heartbeat.

Extrasystoles occur more or less normally throughout life. Many people have them. They occur more frequently with age. In the absence of detectable heart disease, they are of no significance.

The rate of extrasystoles can be increased in normal persons by a great variety of physical, chemical, and nervous stimuli, as well as by many diseases including organic heart diseases. In normal humans, some of the common stimuli are simple pain, emotional stress, fatigue, and chemical constituents of coffee, tea, liquor and tobacco smoke.

People are seldom aware of their extrasystoles under normal conditions, but sometimes the stray beat is noticed and becomes annoying or even frightening. This happens most often when the individual has retired for the night, or is resting quietly. One theory is that extra beats are fostered when the heart rate is slowed; but the extrasystoles would be more noticeable anyway in the absence of outside distractions. A slight momentary discomfort might be detected under the breastbone--a location signaling alarm for many people. When the extrasystoles run close together or when there is another rhythm disturbance with a rapid regular heartbeat, there may be intense fear, sweating, pallor, faintness, nausea and breathlessness.

(more)

EXTRA HEARTBEATS (Cont'd)

Sensations such as these may be the result of heart disease, and call for prompt and detailed diagnostic attention, including medical history, electrocardiogram, and a physical examination.

In the presence of organic heart disease, changes in extrasystole rates may be regarded with concern by heart specialists. For example, during the period of acute heart muscle damage right after a coronary occlusion, the heart rhythm disturbances are the greatest threat of all to the heart attack victim's life. Then the extrasystoles are monitored closely. "Runs" of extrasystoles would trigger real alarms for a coronary care staff.

Extrasystoles in themselves are not evidence of heart disease. When they do accompany organic heart disease the diagnosis of the organic disease is based on findings other than the extra beats.

#

LUNG CANCER--Small cell carcinoma, one type of lung cancer, constitutes 10 to 20 percent of lung cancer cases in the U.S. Studies conducted at the National Cancer Institute show a response rate of 50 percent and some prolongation of survival with a three-drug combination of cyclophosphamide, methotrexate and CCNU [1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea].

#

Photo Feature

RECORD-BREAKING MINORITY BIOMEDICAL SYMPOSIUM HELD

Over 900 undergraduates, graduates, and faculty scientists recently met at the largest United States gathering of minority biomedical researchers. The Third Annual Xavier-MBS Biomedical Symposium in New Orleans was a three-day research conference cosponsored by the NIH Division of Research Resources and Xavier University of Lousiana.

Ciriaco Q. Gonzales, Ph.D., acting director of the NIH Minority Biomedical Support Program (MBS), stated that, "The nation has not utilized the scientific talent of its minority students." There are only 1,200 full-fledged minority scientists in the nation today. The MBS program intends to double this number in four years.

The increase in biomedical research by minority investigators was clearly demonstrated by the presentation of 265 scientific papers at the 1975 Symposium. In 1973, only 70 papers were presented. The papers, representing research from 85 institutions in the nation, covered subjects ranging from virus interaction on nerve tissue to the analysis of waste effluents in waters surrounding a major city.

In June 1972 the MBS program, created by NIH, boosted medical research in minority institutions by using a $2 million budget. Now grants total over $7 million and 75 colleges and universities are involved. Approximately 1,800 student researchers and faculty scientists are participating in the program.

Some research studies currently conducted under MBS are:

* The effects of anti-leukemic, anti-cancerous, and anti-tumorous drugs on living cells (Norfolk State College, Virginia).

(more)

SYMPOSIUM (Cont'd)

- A new technique for identification of specific viruses (Texas A & I University, Kingsville).
- Animal studies evaluating physiological effects on the body after removal of a portion of the liver (Central State University, Wilberforce, Ohio).
- Side effects of oral contraceptives in certain animals (Tennessee State University, Nashville).
- Temporary arrest of malignant tumors and cancer in a susceptible strain of rats (Elizabeth City State University, New Jersey).

Keynote speaker Thomas G. Bowery, Ph.D., Director of the NIH Division of Research Resources, encouraged more minority involvment in research. He told Symposium participants, "The early glimmer of the creation of the MBS program has become an idea and is now slowly becoming a series of facts and realities for many of you."

Researcher Bobby Calhoun of Florida A&M University delivers his paper on "Studies on Salmonella and Shigella Populations in Waterways Surrounding the John F. Kennedy Space Center" at the recent Third Annual Xavier-MBS Biomedical Symposium held in New Orleans. A record total of 265 science papers, presented by minority student and faculty biomedical investigators, was established at the Seminar which was cosponsored by NIH's Division of Research Resources and Xavier University of Louisiana. (NIH Photo #1420)

(more)

SYMPOSIUM (Cont'd)

Undergraduate researcher Estelle Blanchet of Xavier University of Louisiana compares notes with NIH Division of Research Resources Director, Dr. Thomas G. Bowery, at the recent Third Annual Xavier-MBS Biomedical Symposium in New Orleans. Close to 600 active Minority Biomedical Support Program student scientists participated in the record-breaking annual seminar.(NIH Photo #1421)

#

Research Illustrated

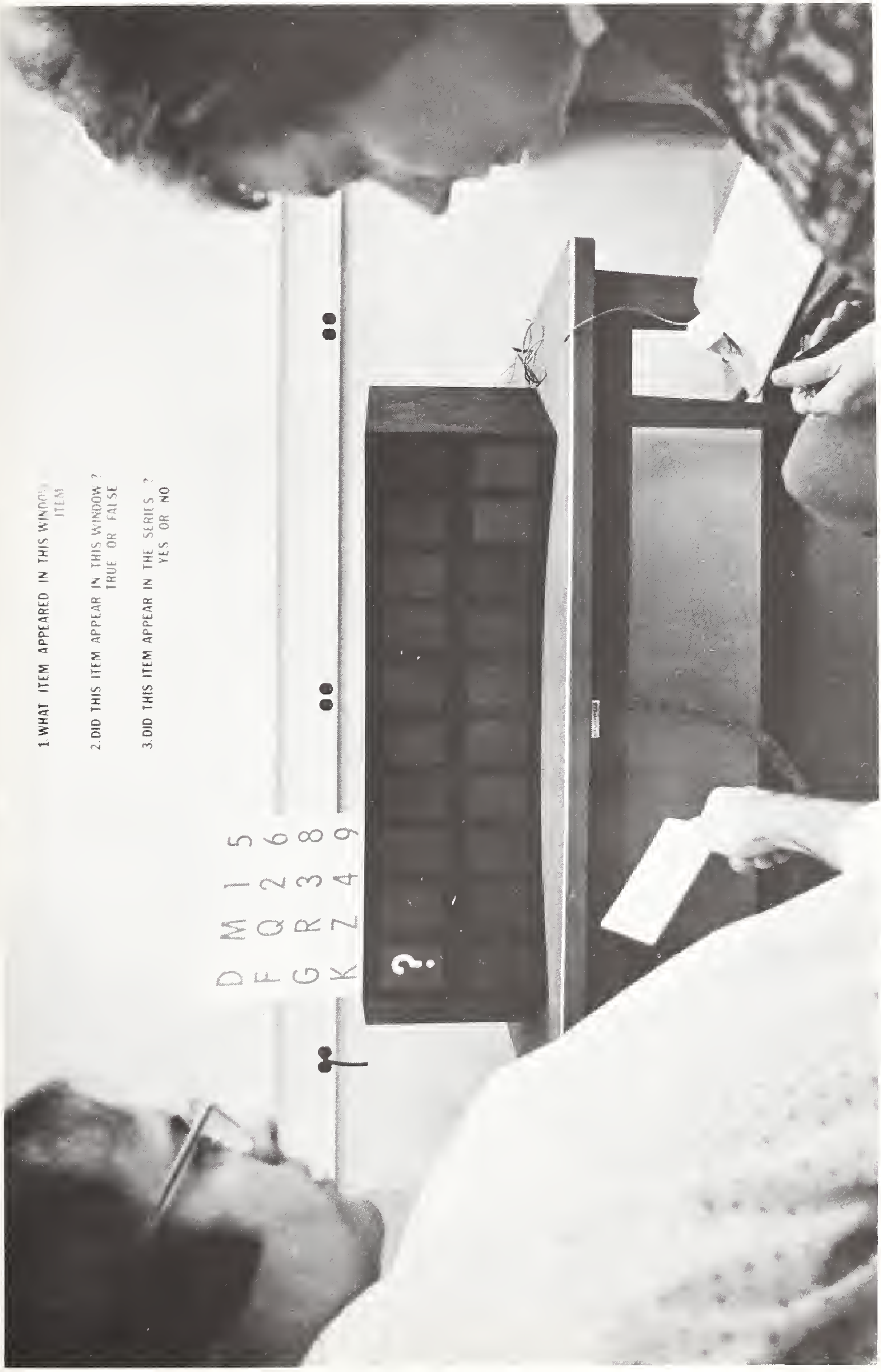
AGING PROCESSES ARE STUDIED AT NIH GERONTOLOGY RESEARCH CENTER

The Gerontology Research Center (GRC), Baltimore, remains the focal point for research on the aging processes within the National Institutes of Health. The scientists, technicians and supporting staff of the Center study the physiological, biomedical and behavioral aspects of aging in both humans and a number of animal species. Their overall goal continues to be directed toward gathering fundamental knowledge of aging that can be used effectively by physicians, other professionals, and the public to enhance the quality of life for all older people. The Baltimore Center, in addition to its own programs, houses a guest scientist contingent with non-government personnel working on projects related to aging, or the illnesses that afflict older people most frequently. In one project, the Center has developed tests to determine the effects of age on bodily strength. This volunteer visits periodically to have his arm and shoulder muscle power measured.

(NIH Photo #1422)

(more)

AGING RESEARCH (Cont'd)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At the Gerontology Research Center a psychologist (right) tests a volunteer's ability to recall and recognize figures and letters. The Center conducts numerous studies on the body's physiological changes that come with age. (NIH Photo #1423)

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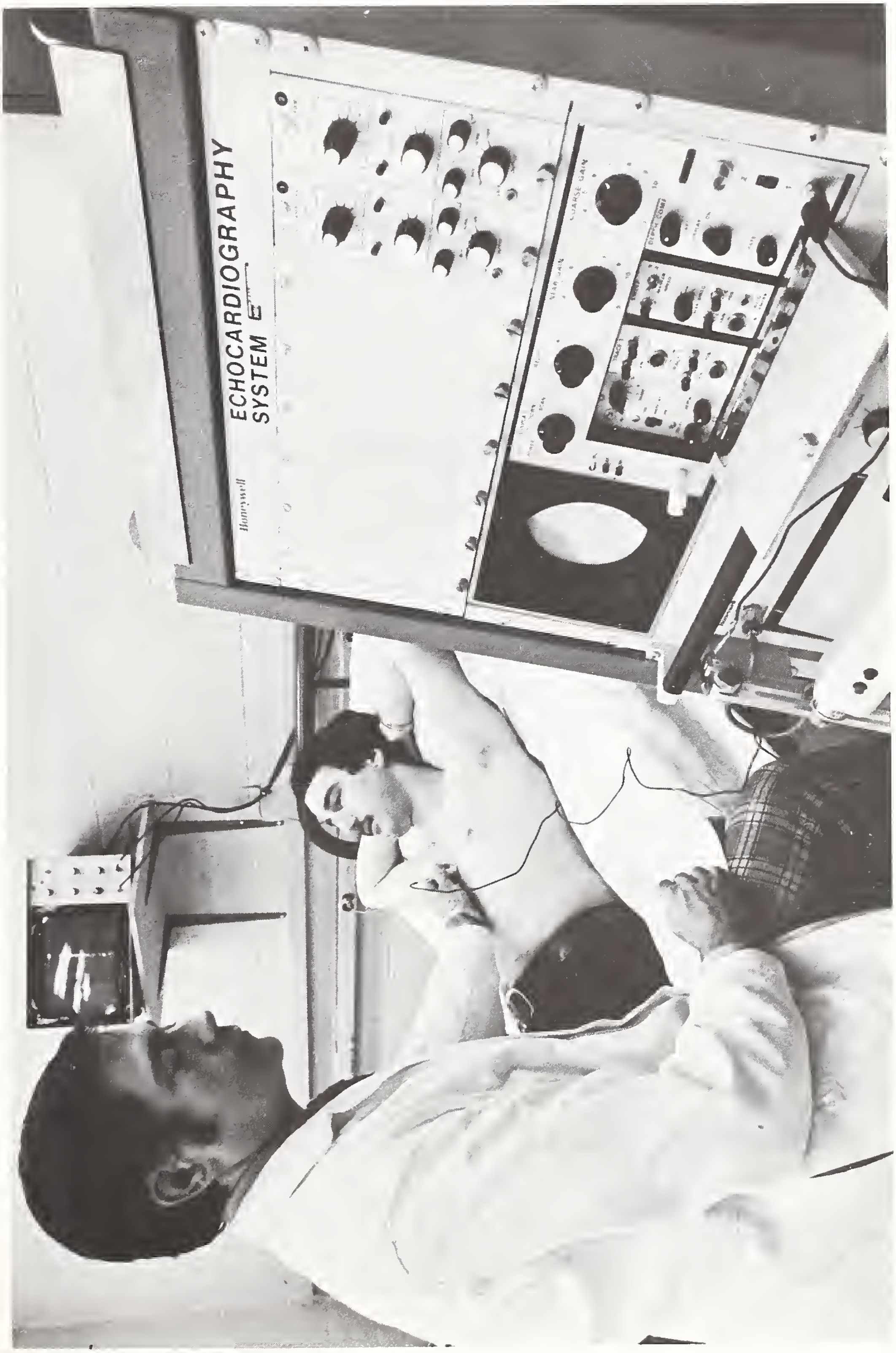
AGING RESEARCH (Cont'd)



A physician at the Center uses an echocardiograph machine to check the heart of this volunteer in a long-term research study. The machine sends out sound waves which are reflected back from the heart and provide images of the heart anatomy. (NIH Photo #1424)

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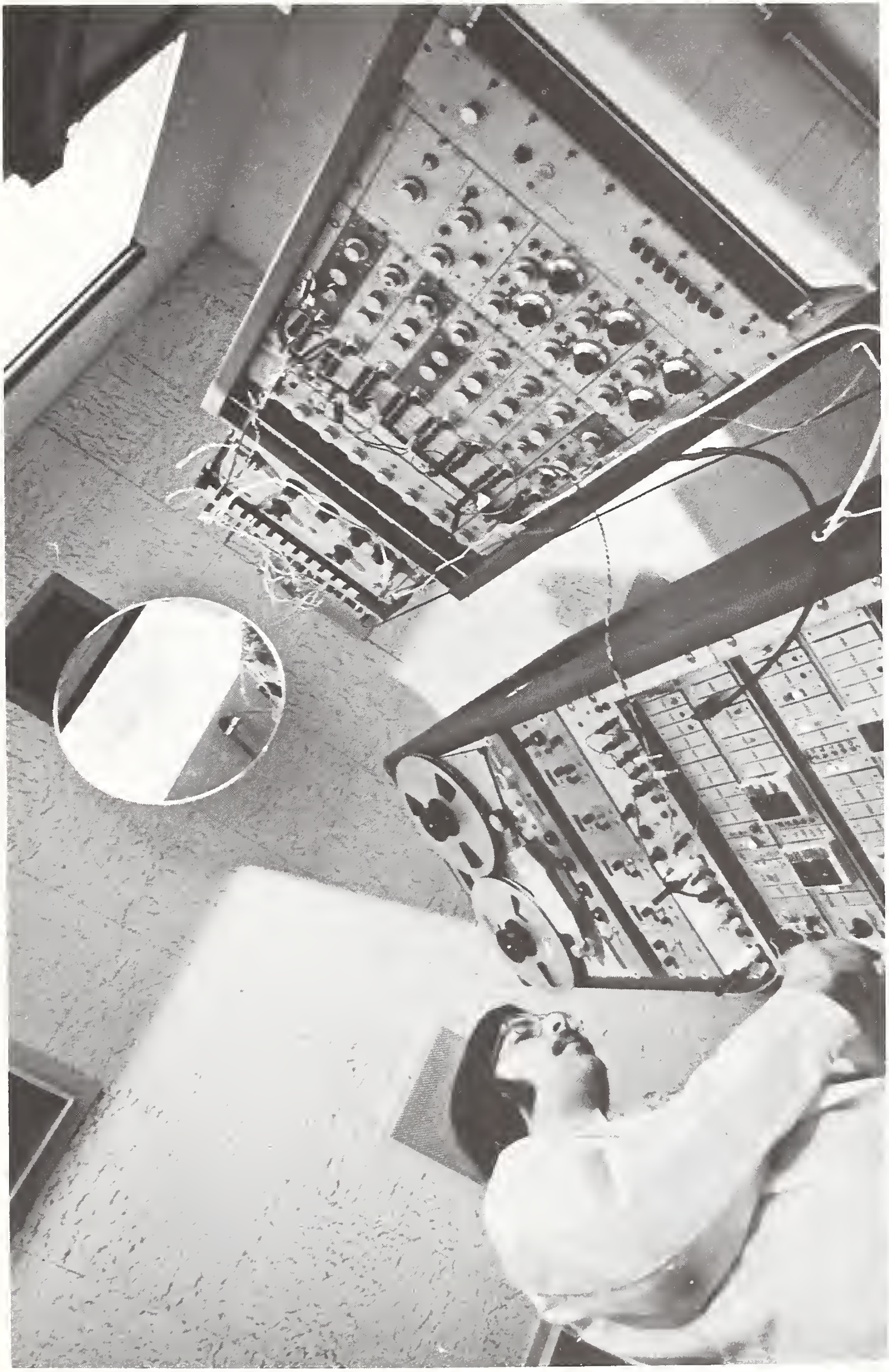

A scientist uses the Center's sophisticated equipment to monitor progress of a patient learning to control his blood pressure. The subject, seen through the overhead mirror, is being taught to raise and lower his blood pressure through operant conditioning and feedback techniques. (NIH Photo #1425)

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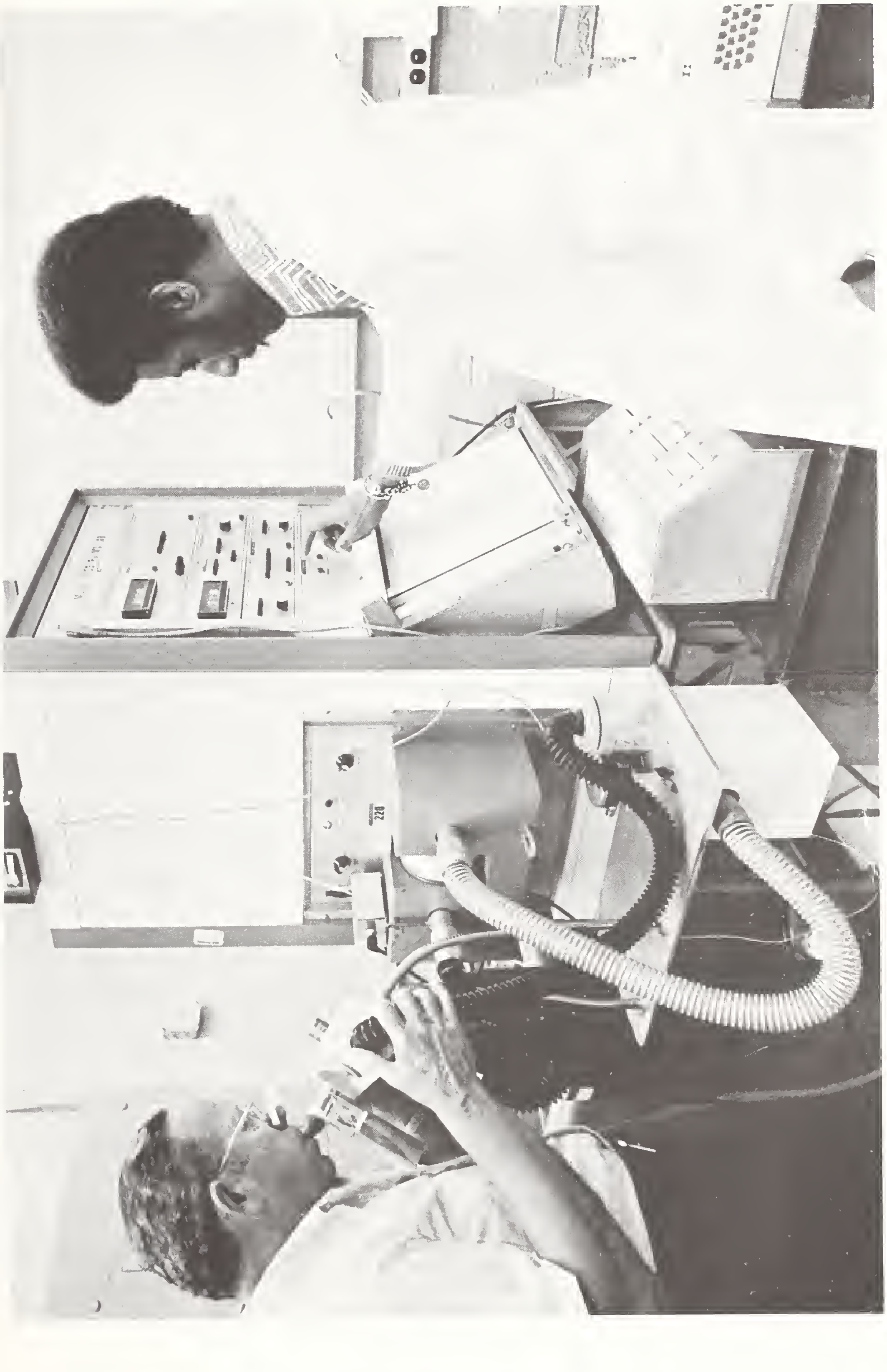
AGING RESEARCH (Cont'd)



The Pulmo-Lab at the Center is used to measure changes with age in the lung function. This subject is one of more than 600 community volunteers taking part in long-term studies of aging at the Center. (NIH Photo #1426)

#

Disease Profile

TICK BITE TRANSMITS ROCKY MOUNTAIN SPOTTED FEVER

Rocky Mountain spotted fever, a tick-borne disease, is caused by the organism, *Rickettsia rickettsii,* which is structurally related to bacteria, but in some of its properties, resembles viruses. The tick bite transmits this spotted fever agent which inflames the inner lining of the blood vessels. As a result, a red spotted rash appears under the skin.

The number of rickettsiae-infected ticks varies from less than 1% to about 5% in most tick-infested areas. In addition to the Rocky Mountain wood tick, *Dermacentor andersoni,* there are other species of hard shell *(Ixodid)* ticks that transmit the disease. Included are the dog tick, *Dermacentor variabilis,* found on the East Coast and *Amblyomma americanum* found in the South.

Spotted fever ticks live in mountainous, heavily wooded or sagebrush areas. The tick season usually runs from spring through early summer although ticks may be seen year round.

An infected tick retains the rickettsiae through subsequent stages in its life cycle; thus, adult females can transmit the organisms through the ovary to their eggs which hatch larvae for the next generation.

Studies also show that many species of animals, particularly rodents, carry the spotted fever agent and transmit it to the ticks that feed on them.

Doctors diagnose spotted fever by the appearance of a rash on the wrists and ankles; however, several days of chills, high fever, headache, and bone pain precede the rash.

(more)

SPOTTED FEVER (Cont'd)

In untreated, severe cases, the fever may persist for several weeks. Central nervous system symptoms such as delirium or coma usually appear by the end of the first week of fever. During the second week, critical circulatory and pulmonary complications may occur. Full recovery commonly takes several weeks or months in untreated patients.

The outlook for spotted fever victims changed radically in 1945 when physicians found the drug--para-amino-benzoic acid (PABA)--to be effective. In the early 1950's, the antibiotics, chloramphenicol and tetracycline, replaced PABA because they were more effective and better tolerated. Today tetracycline is the treatment of choice since it has few side reactions. In the majority of patients when tetracycline is given following prompt diagnosis, the headache and other symptoms abate within 24-48 hours and the fever disappears in 3-4 days. Treatment is usually continued for 24-48 hours after the fever is gone. Relapse may occur in some instances when treatment is initiated very early or is not continued long enough.

A tick must be attached for several hours before it transmits the disease-causing rickettsiae. People in tick-infested areas should examine themselves carefully for ticks, stripping daily and paying special attention to hairy regions. Parents should examine children twice a day.

If a tick is found, it should be removed with care. Pull it off gently with tweezers. Be careful not to crush the tick to avoid contamination of the broken skin with infectious material.

In 1906, when spotted fever was widespread among the settlers of

(more)

Montana, Dr. Howard Taylor Ricketts discovered that the wood tick was responsible for transmitting the fever agent. The settlers eventually turned to the Federal Government for aid, and in 1921, the United States Public Health Service established the Rocky Mountain Laboratory (RML) near Hamilton, Montana. The laboratory quickly became the center of spotted fever and tick-borne disease studies, and there scientists discovered an effective vaccine.

Today, the RML is a part of the National Institute of Allergy and Infectious Diseases. There, in the most modern facilities, scientists study spotted fever in an effort to find answers to fundamental biological questions. The National Institute of Neurological and Communicative Disorders and Stroke also supports research on the effects of spotted fever on the central nervous system--all in an effort to bring this infectious disease under control.

This dog tick, Dermacentor variabilis, *is one of the hard shell ticks that can transmit Rocky Mountain spotted fever. This tick is male. (NIH Photo #1427)*

#

News Releases Issued

SURVIVAL TRENDS--The National Cancer Institute (NCI) has released a report on survival trends among white cancer patients diagnosed between 1960 and 1971 in approximately 100 American hospitals. The NCI scientists have found that survival has improved for some cancers, while remaining essentially unchanged for others. The study measured trends in survival for 48 types of cancer from the 1950s to the 1960s with provisional one-year data on patients diagnosed in the early 1970s.

Data for the report, entitled "Recent Trends in Survival of Cancer Patients 1960-1971," were provided by a group of cancer registries, which have monitored an estimated 10 percent of cancer patients in the U.S. since the 1940s. The report was edited by Lillian M. Axtell and Max H. Myers, Ph.D., of NCI's End Results Section.

One-year, three-year, and five-year survival rates were reported for the 230,502 patients who were diagnosed between 1960-1964 and 1965-1969. One-year provisional survival rates were provided for 45,443 patients diagnosed in 1970 and 1971.

The hospitals in the study included all hospitals in Connecticut, hospitals which treated approximately one-third of the cancer cases diagnosed in California, several hospitals in the Boston metropolitan area, and six large university hospitals in various parts of the U.S.

#

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Research Advances

RADIATION SIDE-EFFECT: DAMAGED SALIVARY GLANDS

Investigators at the University of Texas Dental Science Institute report that radiation sufficient to treat cancer of the head and neck damages salivary glands permanently so that the amount of saliva and its bicarbonate levels are markedly reduced, and therefore such patients need help to prevent tooth decay and to eat properly.

Clinicians have known that dry mouth and a change from low to high levels of decay-causing organisms result from large doses of radiation. But how permanent the changes are, just what chemical changes occur, and ways to counteract these effects are not so well understood.

Supported by a contract from the National Institute of Dental Research, the Texas team collected and analyzed samples of blood and of saliva stimulated by chewing rubber bands from 30 patients (21 men and 9 women) ranging in age from 17 to 76 years (average 55). The samples were taken before and at weekly intervals over a six-week course of treatment. All patients had reasonably good natural teeth and had not been treated for cancer before.

The blood levels of carbon dioxide, sodium, potassium, calcium, magnesium, chloride, inorganic phosphorous, and total protein remained the same before, during, and after radiation. The flow of saliva was reduced over 80 percent during the six-week period of treatment. While most salivary salts became more concentrated than before treatment, the bicarbonates, which enable saliva to buffer bacterial acids, were reduced.

The investigators have found no indications of salivary recovery in their patients even after three years. The patients have had to be carefully guarded

(more)

against tooth decay and also helped with eating problems. During radiotherapy and for several months thereafter they were given more frequent, smaller, softer meals to compensate for the loss of taste and discomfort from dry-mouth eating. The change in eating patterns prevented serious weight loss which would have necessitated feeding by stomach tube.

These findings by Samuel Dreizen, D.D.S., M.D., Lee R. Brown, Ph.D, Sandra Handler, and Barnet M. Levy, D.D.S., were reported at the meeting of the American Association for Dental Research in March, 1975 in New York City.

#

LEUKEMIA--Leukemia is cancer of the blood-forming organs and is characterized by uncontrolled production of abnormal white blood cells. Leukemia may strike at any age, develops each year in about 19,000 Americans, and kills about 15,000, according to the National Institutes of Health.

#

CATARACT SURGERY--Cataract surgery is one of the most successful operations performed today. From 90 to 95 percent of patients undergoing this operation regain useful vision, reports the National Institutes of Health.

#

Research Advances

NEW STUDY HIGHLIGHTS CAUSES OF INTERSTITIAL NEPHRITIS

A recent study supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) has investigated the causes of chronic interstitial nephritis. The research revealed that interstitial nephritis is a common form of chronic renal disease which is rarely caused primarily by infection. The disease is seldom idiopathic and frequently results from analgesic abuse in the United States. NIAMDD grantee Dr. Martin Goldberg and associate, Dr. R. Murray, of the University of Pennsylvania School of Medicine have reported their findings in the *Annals of Internal Medicine*, Vol. 82, No.4, April 1975.

In Dr. Goldberg's study 101 patients with interstitial nephritis were selected from 320 patients with newly diagnosed chronic renal disease. The frequency of etiological factors was calculated. All the patients displayed one or more of the clinical or laboratory characteristics typical of interstitial nephritis.

Interstitial nephritis thus comprised 33 percent of newly diagnosed chronic renal disease. The primary cause of the disorder was clearly identified in 90 of the 101 patients, while 11 patients had "idiopathic" disease. Primary factors noted were: anatomic abnormalities (31), analgesic abuse (20), hyperuricemia (11), nephrosclerosis (10), kidney stones (9), multiple causes (7), and others. Bacterial urinary tract infection was present in 27 patients. However, all these patients had another primary preceding cause of renal damage.

The researchers discovered that 20 percent of new cases of interstitial nephritis resulted from analgesic abuse nephropathy. Such a diagnosis seldom

(more)

was made initially. Either the patient denied analgesic abuse, or the primary physician did not obtain the correct history. Analgesic abuse thus is a common cause of interstitial nephritis in the United States, as it is elsewhere. It was observed that family members other than the patient may also abuse analgesics and suffer from nephropathy. Two of the 20 cases in Dr. Goldberg's study had such a positive family history.

#

CLOGGED ARTERIES--Hardening of the arteries sets the stage for many strokes by clogging arteries carrying blood to the brain. The damaged artery or arteries may be located either inside the brain or in the neck, according to the National Institutes of Health.

#

HYPERTENSION--Hypertension, or high blood pressure, afflicts at least 23 million Americans, reports the National Institutes of Health. High blood pressure increases a person's risk of having a heart attack, stroke, or developing kidney disease.

#

Research Advances

BETA CELLS THRIVE ON SYNTHETIC CAPILLARIES

In 1972, human cancer cells were cultured inside a miniaturized artificial kidney on its bundles of plastic capillaries. Recently, an adaptation of this technique enabled pancreatic beta cells, cultured on artificial capillaries, to continue to synthesize, store, and release insulin. These capillary units might serve as the basis for the development of an artificial implantable endocrine pancreas and of a model for studying insulin secretory dynamics.

The grantees of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) adapted the technique using pancreatic beta cells of newborn rats. The experimental group of cells was seeded into capillary units--consisting of 100 fibers sealed into the ends of a small glass jacket. Control cultures were seeded into plastic flasks. The cells were cultured on the outside of semi-permeable hollow polymer fibers for up to six weeks. The centers of the fibers were perfused with tissue culture medium. The glucose concentration of the perfusate was varied.

Generally, the capillary units released greater amounts of insulin than the control flasks. When the glucose concentration of the perfusate was tripled, there was a fourfold increase in the quantity of insulin released. When the glucose concentration was lowered, there was a large reduction in the insulin released. Seeding of capillary units with "concentrated" beta cells produced even more insulin. Staining of the capillary bundles revealed clusters of viable beta cells with many insulin-secreting granules which were closely applied to hollow fibers. This appears similar to tissue cells found bunched around natural capillaries.

(more)

BETA CELLS (Cont'd)

The NIAMDD grantees, Drs. William L. Chick, Arthur A. Like, and Vilma Lauris, of the Joslin Diabetes Foundation, Boston, reported their findings in the May 23, 1975, issue of *Science*. The data indicate that beta cells cultured on artificial capillaries continue to successfully synthesize, store, and release insulin. The insulin release can be modified by altering the glucose concentration of the perfusate. Cells cultivated in this manner are protected by a membrane barrier and are not vulnerable to immune rejection. Thus, these capillary units might possibly be a prototype for development of an artificial endocrine pancreas.

#

COLLATERAL CIRCULATION--Nature has her own remarkable way of averting disaster even though the coronary arteries have started to harden--"collateral circulation." Neighboring arteries carry more blood than formerly to compensate for a narrowed vessel, and new arterial branches open up to help transport blood to where it is needed, according to the National Institutes of Health.

COMPUTERS--Computers at the National Institutes of Health can monitor a post-surgery patient's heart rate and blood pressure 200 times a second.

#

Research Advances

INFANTS GET FIRST DECAY-CAUSING INFECTIONS FROM THEIR MOTHERS

Boston scientists report that a study of 138 infants from three weeks to 14 months of age showed that *Streptococcus mutans*, chief suspect in tooth decay, did not usually colonize in the mouth until after the first teeth erupted. However, two infants who wore plastic appliances constantly because of palatal clefts developed this infection before their teeth appeared. Eight others who wore theirs only for feeding showed no signs of these bacteria. The work is supported by the National Institute of Dental Research.

Because *S. mutans* is not easy to implant in humans yet is closely associated with caries, scientists need to know when and how it is transmitted. Ordinarily, it is found only in people and a few animals, thus it is not likely to be acquired from their surroundings.

In previous studies made without the help of the new selective MBS agar medium, *S. mutans* was not retrieved until after molar teeth appeared. Another study reported that these bacteria were present in month-old infants on the basis of a fluorescent antibody technique that did not exclude other streptococcal cross-reactions.

In this research, the babies were divided into groups according to whether or not they had teeth. The predentate group included 91 normal babies, and ten with cleft palates. Among these 101 infants, the bacteria were isolated only from swab samples in the two cleft infants who wore their appliances constantly.

Forty other babies, all normal with incisor teeth only, were sampled twice. Twenty-three of them had their mouths swabbed. Also, the upper two-thirds of their teeth away from the gum line were scraped with a sterile curette.

(more)

DECAY (Cont'd)

Seventeen others were swabbed, and plaque was also scraped from the lower third of the teeth closest to the gum line. Swabbing retrieved *S. mutans* from only one infant with teeth. Later this child had all upper incisors extracted because of rampant decay. *S. mutans* was isolated by scraping the upper parts of the teeth in only one infant, whereas scraping near the gum line retrieved it from eight of the 17 (47 percent) babies. These results show how selective *S. mutans* is in its habitat, and the importance of knowledgeable sampling for surveys.

In all cases, the first variety of *S. mutans* found was serotype C. In a few infants sampled several times, the organism did not appear until ten to 12 weeks after the first incisor erupted.

Populations of *S. mutans* were compared in nine pairs of mothers and infants. Again the C serotype was most common among mothers, but one B, two D, and one E serotype were also found. Since the B serotype is quite rare, that mother's infant was sampled again some weeks later, and by then the B type was also retrieved from her baby.

The investigators consider that their findings indicate that children get their first decay-causing infections from their mothers, that this particular organism requires a hard surface on which to colonize successfully.

Robert J. Berkowitz, D.D.S., of Harvard School of Dental Medicine, Harold V. Jordan, Ph.D., of Forsyth Dental Center, and George White, D.D.S., of Tufts School of Dental Medicine reported this research in the *Archives of Oral Biology*, March 1975.

#

Research Advances

NEWBORNS CAN DISTINGUISH TASTES, MAKE PREFERENCES

Newborn infants do not lack the capability to distinguish and do prefer certain tastes, according to investigators at a recent symposium on taste in the newborn.

A study conducted by James M. Weiffenbach, Ph.D., of the National Institute of Dental Research (NIDR), and Bradley Thach, M.D., shows that babies are quite competent to sense the world around them, an idea divergent from the traditional thinking that newborns lack the capacity to recognize and use sensory stimuli.

Drs. Weiffenbach and Thach used reflex responses of the tongue to show that newborns can tell the difference between flavored and unflavored water. For the first time they separated responses to touch from those to taste.

The scientists touched one side of the infants tongue with a drop of water every 30 seconds until six successive drops failed to get a response. Then, while maintaining the same intervals, they applied 12 successive drops of a test solution. They tested with several concentrations of glucose and compared the responses of groups of male and female infants six to 30 and 30 to 72 hours old. They tested a total of 48 infants.

In additional studies, babies received drops of glucose solution first, and then were tested with drops of water. The tongue responses indicated that drops of plain water and drops of a sweet solution were equally effective in reducing subsequent responses to drops of water, showing some receptors respond to both fluids.

After the response to plain water drops stopped, the infants' tongues

(more)

still responded to glucose, indicating that the newborn have another type of receptor which responds to flavor. As the concentration of the taste substance increased, the infants responded more frequently, showing that they can discriminate among degrees of sweetness.

The tongue responses were much the same for the first three days of life although males gave more orderly and predictable responses than females. Additional studies with salt solutions showed similar patterns of discrimination. All of the reactions were separate from the process of eating, a more complex problem.

The investigators presented a report of their research during the annual meeting of the Eastern Psychological Association in April, 1975. This symposium stemmed directly from a conference held last summer on the Development of Sweet Preference which was jointly sponsored by NIDR and the Fogarty International Center.

#

HUMAN BODY--The mature human body is the end result of nearly 20 years of growth. Each individual begins as the product of two cells and eventually is made up of 100,000 billion cells, according to the National Institutes of Health. The most rapid and crucial period of growth in the human being occurs in the nine months before birth.

#

Photo Feature

COMPUTER-BASED SYSTEM IS USED TO CORRECT SPEECH ARTICULATION ERRORS

Scientists at the Outpatient Clinical Research Center at the University of Alabama in Birmingham (UAB) use a new computer-based instrumental system known as PAGIS to diagnose and treat speech defects as well as study normal speech patterns. With this system, the researchers detect and measure the pattern of tongue contact against the roof of the mouth and the motions of the lips and jaws during the actual processes of speaking. Their study is under the direction of Samuel G. Fletcher, M.D., chairman of the Department of Biocommunication at UAB Medical Center, and is funded by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).

Tiny electrodes or "beads" embedded in a thin plate are placed against the roof of the mouth to detect tongue contacts while a video-based system determines lip and jaw activities by scanning and measuring the "beads" attached to the face and one tooth. A computer takes in all the information, processes it and displays it back to a clinician or, in many instances, to the speaker himself. This feedback system may offer assistance to patients who are not helped through the traditional techniques of speech therapy.

In one case, an hour's therapy using PAGIS helped a patient begin to produce a normal "s" sound by being able to see a visual display of his tongue, lip, and jaw placement. He had received speech therapy for three years, but the traditional methods had not corrected the problem.

The investigators programmed the computer to display the pattern of a normal "s". As the subject spoke, lights on a display panel in front of him lit as he touched different spots on the roof of his mouth. This allowed

(more)

SPEECH (Cont'd)

him to see as well as feel what was happening in his mouth. He compared this pattern with what the computer showed him to be correct. As he changed his pattern of speaking to produce the normal display, he felt and heard the results. In this way he changed his speech rapidly and later used his own sensing to continue to speak correctly.

At the Outpatient Clinical Research Center, scientists in the fields of speech pathology, experimental phonetics, physiology, dentistry, and electrical engineering work together in a pioneering effort to increase understanding of the physiological processes and disorders of speech articulation.

Dr. Fletcher and his daughter Jennafer demonstrate the new computer-based instrumental system PAGIS. PAGIS is now in use at the Outpatient Clinical Research Center at the University of Alabama in Birmingham. (NIH Photo #1428)

#

Photo Feature

ADVANCES REPORTED IN RESEARCH ON ALLERGY

The National Institute of Allergy and Infectious Diseases (NIAID) estimates that 17 out of every 100 Americans -- more than 35 million persons -- suffer from one or more allergic disorders. Basically, an allergy is a hypersensitivity acquired through exposure to a particular allergen. Some common allergens are foods, pollens, mold spores, drugs, animal danders, insect venoms, and house dust.

Allergic responses are similar to reactions which protect us from infectious diseases. In both cases, antibodies are usually produced and circulate in the blood. During an infection, these antibodies fight and kill the invading microorganism. In an allergic reaction, antibodies sensitize the subject to a substance. With each reexposure to the allergen, more antibodies, called immunoglobulin E (IgE), are produced. Eventually the symptoms of allergy are triggered whenever the allergen is encountered.

It is not completely understood how antibodies cause allergy symptoms. Since the isolation of the chemical mediator, histamine, more than 40 years ago, NIAID grantees have been researching the sequence of events which occur in allergic reactions.

One of the most important advances in allergy studies was the isolation of IgE antibodies in 1966 by NIAID grantees Drs. Kimishige and Teruko Ishizaka, formerly at the Children's Asthma Research Institute and Hospital in Denver. Scientists now know that IgE stimulates sensitized tissue cells, called mast cells, to release chemical mediators. These mediators, in turn, lead to the varied symptoms of allergy, such as nasal swelling and congestion.

(more)

ALLERGY (Cont'd)

A NIAID grantee, Dr. K. Frank Austen of Robert B. Brigham Hospital in Boston, has researched a control mechanism of the acute allergic reaction. Eosinophils, a type of white blood cell found in high levels in allergic patients, contains an enzyme-arylsulfatase 2B. Dr. Austen's group demonstrated that this enzyme inactivates a chemical mediator known as SRS-A, suggesting the enzyme may have some control over the allergic reaction. Varying degrees of this enzyme's efficiency may account for differences in the severity of allergic reactions. The enzyme inactivation of SRS-A has not been demonstrated to occur in nonallergic people.

In 1971, the NIAID initiated its Asthma and Allergic Disease Center (AADC) program. The program is designed to transform the application of fundamental knowledge of immunology into improved methods of patient therapy. The grants permit the Centers to establish clinical studies in immunology, primarily on an out-patient basis. There are 17 Centers in the United States.

NIAID has a contract program for preparing research materials needed by investigators. Ragweed antiserum and three allergenic components of ragweed have been produced and are undergoing certification. In 1974, the production began on antisera for human IgE which could be used for an allergy test, the radioallergosorbent technique (RAST). Also in 1974, work began on the establishment of an allergen certification laboratory.

AADC Director Dr. Gerald J. Gleich of the Mayo Foundation Graduate School of Medicine in Rochester, Minnesota, is studying the factors controlling the production of IgE. His findings on patients with ragweed hay fever appeared to support the theory that the severity of a patient's allergic disease is related

(more)

to his IgE antibody levels. Dr. Gleich is now evaluating the effect of allergy shots on IgE levels during the course of a year.

Asthma, a noncontagious disease of the bronchial tubes, affects an estimated 9 million Americans. Normally, the airways offer little resistance to the air flow. During an asthmatic attack, the bronchial lining becomes swollen with fluid, viscous mucous blocks the small tubes, and spastic contractions of smooth muscles in the lungs close down practically all the bronchial passageways. Breathing becomes labored, and the rush of air through the narrowed passageways gives a wheezing sound.

Dr. Robert G. Townley, director of the Center at Creighton University, uses methacholine and histamine to test the airway sensitivity of certain patients. He used the test to determine which people, predisposed to allergy, are at high risk of developing asthma. Dr. Townley accurately predicted the onset of asthma in several subjects. If identification of potential asthmatics were possible, physicians could provide patients with valuable preventative measures including advice concerning occupational and environmental hazards.

Allergic rhinitis, or hay fever, is an allergy commonly caused by inhaled pollens of trees, grasses, or weeds. An estimated 14.6 million Americans are hay fever sufferers. Common therapy is immunotherapy, or "allergy shots," which increase the patient's tolerance for the pollen to which he is allergic. Diluted extracts of pollen are injected. Dosages are gradually increased and given less frequently. The size of the largest dose is determined by the patient's tolerance and the therapy's effect on his symptoms. It may take several years for a significant reduction of symptoms to take place.

(more)

ALLERGY (Cont'd)

Dr. Roy Patterson of the AADC at Northwestern University is investigating the use of only a part of an allergen in injections. The chemical breakdown of crude ragweed has isolated four fractions -- antigens E, K, Ra3 and Ra5. Dr. Patterson prepared a polymerized form of antigen E and is using this material in immunotherapy. If proven effective, the use of these materials could lessen the number of injections needed, saving the patient considerable time, money and discomfort.

Bees, yellow jackets, wasps, hornets, and fire ants are some of the stinging insects that can cause dramatic allergic reactions. A single sting to a sensitive person may lead to a serious drop in blood pressure, shock, and possibly death. There are more than 50 reported fatalities a year. Undoubtedly more deaths occur but are diagnosed as heart attacks, stroke, or convulsions.

For years, physicians have treated these patients by immunizing them with whole insect body extracts. This treatment is not always successful. Dr. Philip S. Norman and associates at Johns Hopkins University have shown that whole bee venom, as opposed to whole- body extracts, is significantly more accurate in diagnosing an insect sting allergy. In a small number of patients, honeybee venom extract appeared to supply better protection. In a treatment study of yellow jacket venom, similar positive results were noted.

Dr. Carl E. Arbesman and associates at the State University of New York, Buffalo, evaluated the RAST test for use in diagnosing insect sting allergy. Using bee venom and whole-body extracts, they showed that the RAST test is very specific safer than skin tests, and more accurate. The test may also prove useful in determining when to start or stop immunotherapy.

(more)

Dr. Willard Elliott at the State University of New York, Buffalo, and other scientists are investigating new techniques for obtaining the scarce insect venoms needed for research.

Allergies affecting the skin take many forms, the most common being eczema, urticaria (hives), angioedema, and contact dermatitis. Foods, cosmetics, fabrics, metals, and plant resins are the most common causes.

AADC Director, Dr. Rebecca H. Buckley of Duke University Medical Center, is studying the role of cellular immunity in allergies. Cellular immunity utilizes lymphocytes of thymic origin to combat foreign materials in the body. Patients with allergic eczema have a high amount of detectable IgE. In these patients, Dr. Buckley found depressed cellular immune responses correlated with the extent and severity of the eczema. This finding supports the theory that excessive production of IgE may be associated with a deficient cellular immune function in patients with allergic disorders.

Dr. Allen P. Kaplan, Director of the AADC in the NIH Clinical Center, is studying urticaria resulting from exposure to cold. The allergy to cold results in hives and may also lead to a drop in blood pressure, fainting, severe shock, and sometimes death.

Dr. Kaplan found that cold urticaria results from histamine released from body tissues as they begin to warm up after a cold stimulus. Extremely high histamine levels coincided with episodes of very low blood pressure, the cause of fainting. Dr. Kaplan identified IgE in the blood of these patients. He purified it and is now studying its mechanism of action in cold urticaria.

Pulmonary diseases resulting from exposure to inhaled fungi, chemicals, and

(more)

ALLERGY (Cont'd)

organic dusts are of increasing concern. The Center at Louisiana State University, under the direction of Dr. John Salvaggio, is investigating the immune mechanisms of the lung.

Hypersensitivity lung disease causes shortness of breath and weight loss. It often develops in workers who are exposed to organic dusts. Beryllium, asbestos, and TDI (toluene diisocyanate, used in the plastics industry) are other substances suspected of causing the disease.

Dr. Salvaggio has been able to reproduce the lung damage and certain immune responses of the human disease in rabbits. Results of his research indicate that the particle-like nature of the mold antigen is important in the production of the disease. The antigen is insoluble. Thus, body cells ingest it but cannot dissolve it. Diseased areas form, similar to the way a pearl forms in an oyster.

#

A patient with cold urticaria will develop a wheal at the site touched by an ice cube. (NIH Photo #1429)

News Feature

NORMAL VOLUNTEERS ARE HOSPITALIZED AT NIH BECAUSE THEY ARE HEALTHY

"Normal Volunteers" are healthy patients in the NIH research hospital, the Clinical Center. By studying the volunteers, physicians learn more about normal physiology and metabolism. This knowledge leads to better understanding of abnormal body function, and sometimes to new treatment for disease.

From their participation, volunteers gain a unique life experience through contributing to better health, increased understanding of hospital patients and staff, and often, on-the-job training in a career in the health field.

Over 4,000 patients, referred by their own doctors, are admitted to the Clinical Center annually. These patients are selected by NIH physicians because they have a stage of disease needed for the research programs. Volunteers, under the sponsorship of colleges, civic organizations, and religious groups, are also admitted as patients. They totaled about 380 patients in 1974.

The studies in which volunteers participate reveal information about a variety of normal body functions ranging from sleep or the effects of diet, exercise, and chemicals on metabolism, to biofeedback.

In one recent study, volunteers were confined to their rooms twice a week for 24-hour blood pressure measurements. In another, volunteers covered one eye and indicated when they saw a light projected on a screen. Their reactions were compared to those of patients with vision disorders. In still another study, volunteers breathed into a machine that measured lung volume and airflow rate. The results were compared to those of patients with lung disease.

In all studies, patient safety is the first priority. Like other patient research, volunteer protocols are carefully reviewed by several multi-disciplin-

(more)

ary committees as well as the NIH Director to insure volunteer safety. Physicians and other members of the hospital staff are competitively selected and screened for superior qualifications. No dangerous or unknown procedures are followed, and no serious mishap has occurred since the beginning of the program in 1954.

Each step in a study is explained in detail well in advance and signatory consent is required from all patients before their participation may begin. Most volunteers remain in the program for about three months; however, they may withdraw at any time.

The precautions taken to safeguard the volunteer's health include, as a fringe benefit, superb medical and dental care. Upon admission to the Clinical Center, each volunteer is given a complete physical examination and a detailed medical history is taken. Another complete physical examination is performed prior to discharge.

As healthy patients, volunteers share a hospital room with one other person, usually another volunteer. They experience the same benefits and restraints as other patients.

Free time is often spent working with NIH scientists in career development programs. Laboratories provide experience in basic, applied, and computer sciences, and ample opportunities exist for future doctors, nurses, and other health sciences professionals to be participant-observers in their chosen field. Opportunities are also available in such facilities as occupational, physical, and recreational therapy services, public information office, medical arts and photography sections, or the library.

(more)

The NIH
Normal Volunteer
Patient Program

Note to Subscribers

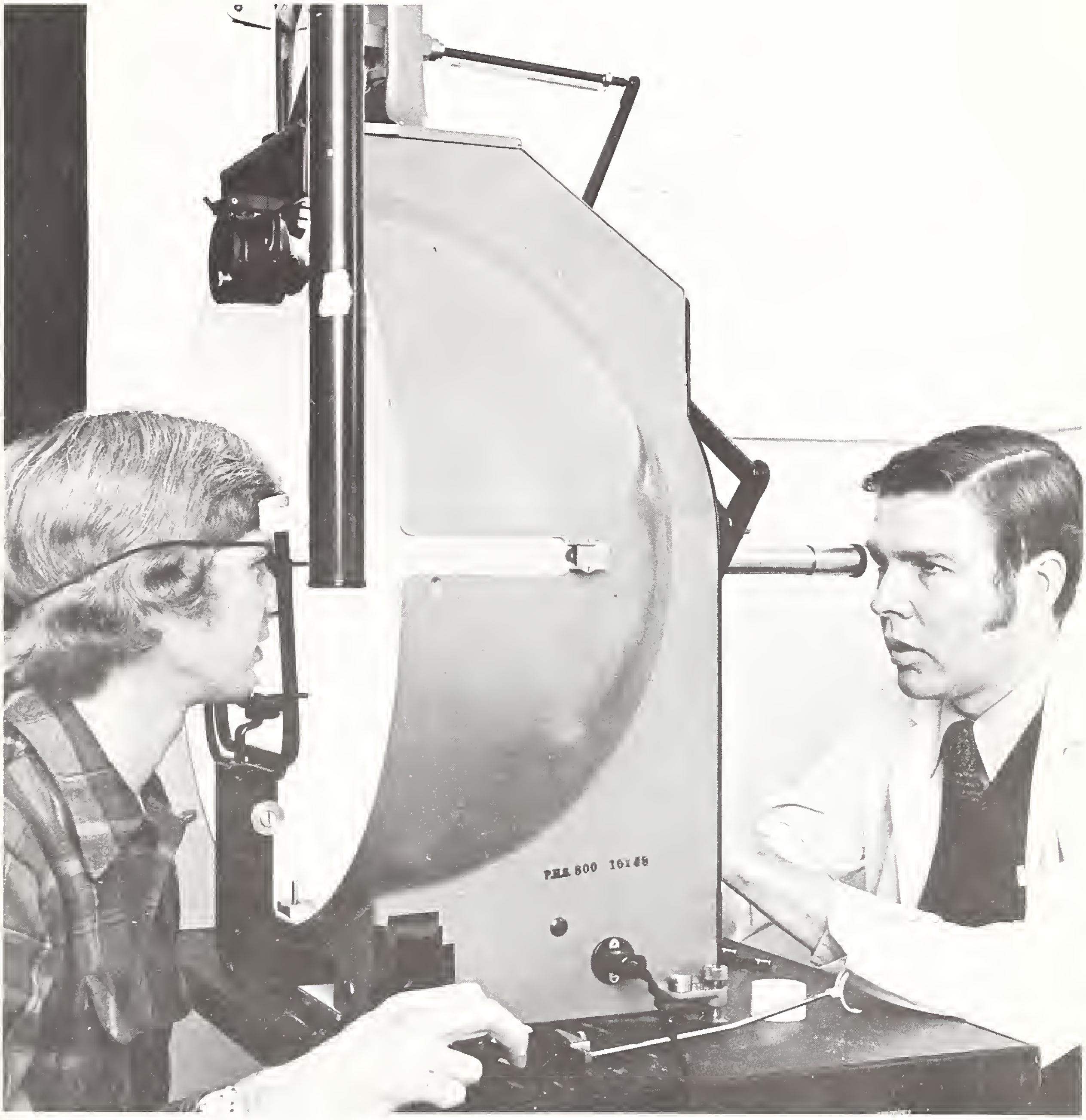
Free copies of this new brochure are available from the NIH Clinical Center, Room 1N-248, Bethesda, MD 20014. More information about the Normal Volunteer Patient Program can be obtained from Delbert L. Nye, Chief, Normal Volunteer Patient Program, NIH Clinical Center, Bethesda, MD 20014, (301) 496-4763.

Of related interest are the photographs that appear in the Research Illustrated story that begins on page 22 of this issue.

#

Research Illustrated

A LOOK AT SOME OF NIH'S NORMAL VOLUNTEER PATIENTS



The healthy patients admitted to the NIH Clinical Center serve as human controls so that physicians can learn more about normal physiology and metabolism. An NIH physician is shown examining a volunteer's eyes. Information about normal vision aids in the investigation of vision disorders. (NIH Photo #1430)

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NORMAL PATIENTS (Cont'd)

Relaxing to aid science are two normal volunteers. They have agreed to day-long measurements of their blood pressure. (NIH Photo #1431)

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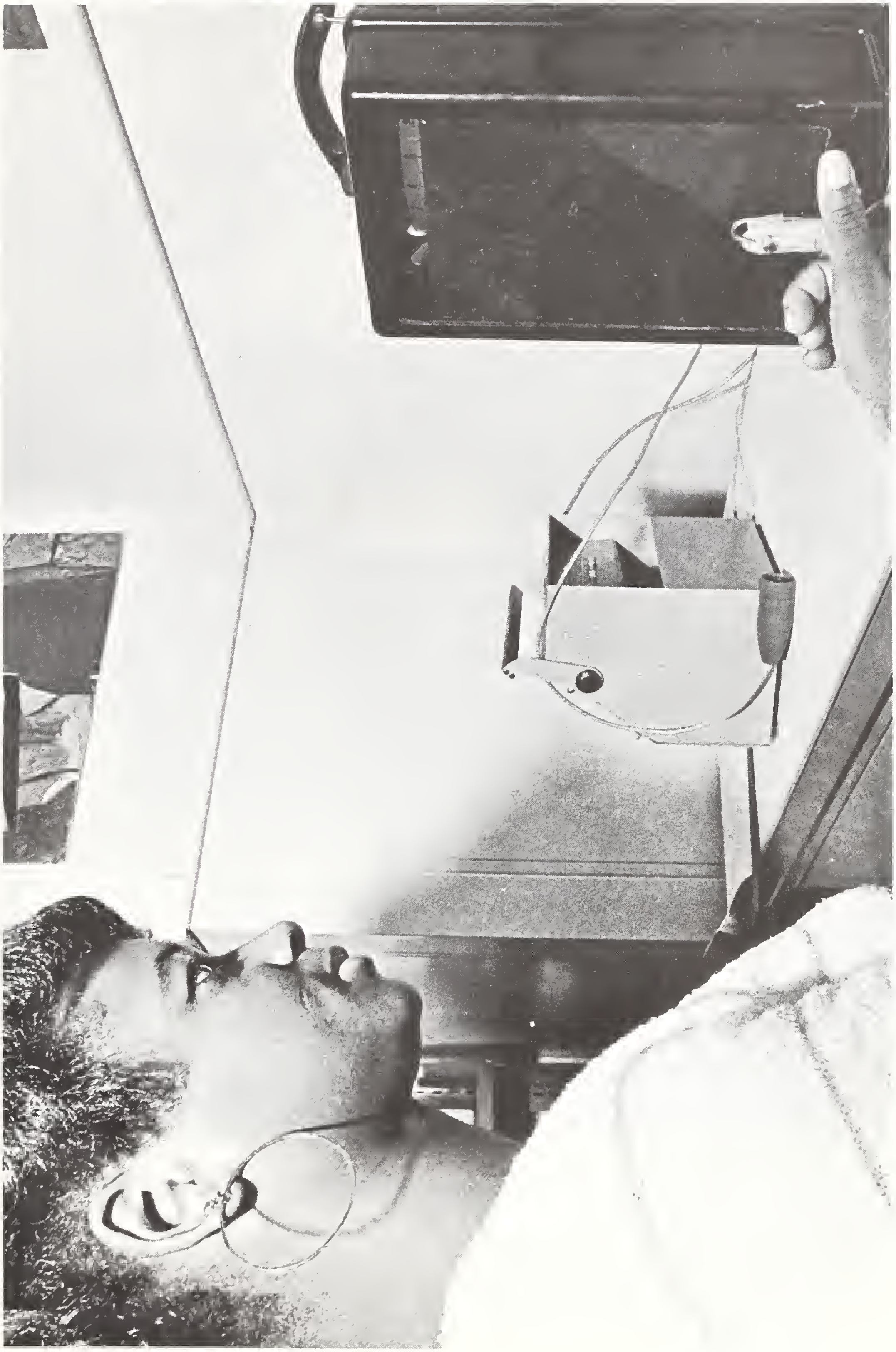

This normal volunteer at the NIH Clinical Center is participating in a biofeedback study. She is considering a career in the health field, and so she is very interested in the tests being conducted on her and on the other normal volunteers she has met. (NIH Photo #1432)

(more)

NORMAL PATIENTS (Cont'd)

A future recreational therapist is planning and directing sports activities for ill patients during the time she is not participating in a metabolism study. (NIH Photo #1433)

(more)

NORMAL PATIENTS (Cont'd)

Laboratory assignments given to normal volunteers, including bench work here and tadpole observing (on cover page), provide insight and experience in health research careers. (NIH Photo #1434)

#

Disease Profile

GONORRHEA REMAINS MOST COMMON VENEREAL DISEASE

The National Institute of Allergy and Infectious Diseases supports many research projects on gonorrhea. Studies are being conducted on the structure and virulence of gonococci, screening techniques, and new methods of treatment and prevention.

Gonorrhea, the most common venereal disease, is caused by the bacterium gonococcus *(Neisseria gonorrhoeae).* The gonococcus often infects the lining of the genitourinary tract. An acute purulent infection will usually be found in the male's urethra and the female's urethra and cervix.

Symptoms of gonorrhea usually begin within two to eight days after exposure by sexual contact. However, many people, especially females, may have no visible symptoms until a much later time. Symptom-free infections may be one reason for the current uncontrolled spread of this disease.

Complications of gonococcal infection often include sterility, arthritis (particularly in the female), brain infection (meningitis), or heart inflammation (endocarditis). Newborn children may acquire an eye infection from a mother's infected birth canal. To prevent infection, silver nitrate solution is placed in the eyes of all infants immediately after birth.

Recent changes in sexual practices may be related to the increasing number of gonococcal infections in areas such as the rectum and throat. Testing for the disease in other parts of the body besides the genitourinary tract has proved important.

Four types of gonococci are divided according to their appearance and growth in laboratory culture media. Types 1 and 2 appear to be "infectious"

(more)

or "virulent." Types 3 and 4 are not usually associated with disease. "Pili," microscopic, hair-like appendages, on the surface of types 1 and 2, are not found on types 3 and 4. Some scientists hypothesize that certain gonococci "hitchhike" on sperm, traveling through the male and female reproductive systems causing local spread of infection.

After the discovery of pili, a sensitive radioimmunoassay test for detecting gonococcal infections was developed. Evaluation of the test is underway. The test is useful in asymptomatic women and may be applied to men with pharyngeal gonococcal infections.

Effective gonococcal therapy depends on early identification. The present method takes four days for growing, isolating and identifying organisms. Harry E. Morton, Sc. D., NIAID grantee at the Hospital of the University of Pennsylvania, recently developed a rapid screening test for detecting the gonococcus. Specially prepared antibody-coated cells are used. The test requires only small amounts of materials, ordinary equipment found in bacteriological laboratories, and no highly skilled personnel.

For more than 30 years, the treatment of choice for gonorrhea has been penicillin. Three years ago, however, the Public Health Service doubled its recommended dose of penicillin in response to increased reports by physicians of treatment failures.

Because of resistance and because an unknown number of Americans are allergic to penicillin, other antibiotics must sometimes be used. Unfortunately, there are reports of gonococcal strains becoming resistant to the "second line" antibiotics -- spectinomycin, kanamycin, and tetracycline.

Some gonococci, when exposed to penicillin, become L-phase variants.

(more)

This means they are not killed, but lose their rigid, shell-like cell walls and continue to multiply as tiny microbes. Since penicillin acts by preventing cell wall formation, it does not harm these defective variants. Scientists suspect that L-phase variants may play a role in gonorrhea treatment "failures" or in "non-gonococcal" urethritis.

#

ARTERY HARDENING--Every artery throughout the body is subject to hardening, but the most often and most seriously affected vessels are the largest arteries, such as the aorta; the coronary arteries, and the arteries that feed the brain and kidneys. Arteries may harden in one part of the body more rapidly than in other areas, according to the National Institutes of Health.

CARDIOVASCULAR SYSTEM--The body's circulatory system--also called the cardiovascular system--is made up of the heart and the arteries, capillaries, and veins. The heart contracts about 70 times each minute, pumping oxygen- and food-rich blood into all regions of the body to nourish the muscles and tissues, according to the National Institutes of Health.

EARLY START--Hardening of the arteries may actually begin in early youth, perhaps even at birth. How troublesome it eventually becomes varies with each individual who has it. Some escape any consequence of the condition whatsoever. Others develop some symptoms, but with proper medical care continue normal and productive lives, according to the National Institutes of Health.

#

News Releases Issued

IUD USE--The National Institute of Child Health and Human Development (NICHD) has announced a $300,000 contract with The George Washington University for the collection and analysis of data concerning the use of intrauterine contraceptive devices (IUD's). The University will gather information on problems resulting from the use of these contraceptive devices, as a number of serious side effects have been reported.

Although intrauterine devices of several designs are currently used as a birth control method by more than three million American women, the precise rates of major and minor complications of use are not well established. Minor complications of use are device expulsion, discomfort, and bleeding. More serious events include pelvic inflammatory disease, hemorrhage, uterine perforation, ectopic pregnancy, and septic second-trimester abortion.

Heinz Berendes, M.D., chief of the Contraceptive Evaluation Branch, NICHD Center for Population Research, said that the study results are intended to assess relative risks of severe complications to each type of IUD in present use in the United States. Since serious complications are expected to occur infrequently, data from several sources will be pooled. The Department of Biostatistics of The George Washington University will collect, validate, and analyze data from at least 10 participating clinical facilities.

- - -

FLU LAB--The National Institute of Allergy and Infectious Diseases (NIAID) has established a special influenza laboratory at St. Jude Children's Research Hospital, Memphis. This laboratory will serve as the focus for an international network of investigators checking on influenza infections in animals.

Knowledge gained by the scientists at St. Jude Children's Research Hospital

(more)

should define the relationship between animal and human influenza viruses, possibly explaining the mysterious periodic appearance of epidemic human influenza viruses. This, in turn, will help other investigators prepare for human influenza pandemics (worldwide epidemics), according to NIAID.

The laboratory will be under the direction of Dr. Robert G. Webster, a member of the Laboratories of Virology and Immunology at St. Jude Children's Research Hospital.

- - -

INJECTABLE CONTRACEPTIVE--As part of its continuing commitment to provide safe and effective alternative methods of contraception, the Center for Population Research of the National Institute of Child Health and Human Development has awarded a $1.2 million cost-sharing contract to Schering AG of Berlin/Bergkamen in the Federal Republic of Germany to develop a long-acting injectable contraceptive agent for females.

The contract calls for the testing of norethindrone enanthate--the parent compound of which is now used in oral contraceptive agents--according to FDA guidelines. Schering AG now holds the patent for the drug. Norethindrone enanthate has demonstrated effectiveness in preventing pregnancy for up to 12 weeks following a single injection. Side-effects include breakthrough bleeding and spotting, with alteration of the menstrual cycle. These side-effects appear to diminish with continued use of the contraceptive.

Although many animal and human investigations have already been conducted with norethindrone enanthate, additional studies must be undertaken to satisfy FDA requirements to market the drug in the United States.

#

Editors of publications may request a glossy print of the numbered photographs that appear in this issue.

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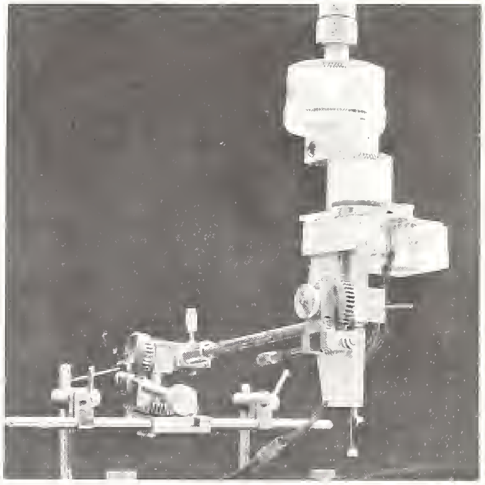

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NEWS & FEATURES From NIH August 25, 1975

Research Advances

MANUFACTURE OF ARTIFICIAL ANTIBODIES IS RESEARCH GOAL

Recent findings by NIH scientists are contributing to an international effort that may eventually make possible the manufacture of artificial antibodies.

The NIH researchers are helping to define the three-dimensional structure and chemical make-up of antibodies, proteins critical in the body's defenses against bacteria, viruses, and other foreign substances.

Other centers active in this research include the Max Planck Institute, Munich, Germany; the Johns Hopkins Medical School, Baltimore; and the Argonne National Laboratory, Argonne, Illinois.

In the newest edition of the "Annual Review of Biochemistry," NIH scientists David R. Davies, Ph.D., and Eduardo A. Padlan, Ph.D., of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), and David M. Segal, Ph.D., formerly of NIAMDD and now at the National Cancer Institute (NCI), summarize recent antibody research and describe X-ray crystallographic evidence of remarkable similarities in the complex structure of antibodies from humans and mice.

NIH findings are consistent with previous descriptions of antibodies, the proteins produced by certain white blood cells called plasma cells. An antibody is a three-lobed structure with considerable flexibility, containing two short and two long chains of protein. It is "hinged," so that it can pivot from a taut T-shape to a forked Y. (See illustration on page five)

The NIH investigators have found that the "business ends" of the antibody in trapping foreign substances are the distant ends of the T's crossbar and of the Y's upraised arms. Their evidence came from a series of experiments

(more)

on antibody fragments that bind a foreign substance called phosphorylcholine. In these experiments phosphorycholine was trapped in a cleft between the short and long chains at the outermost area of the T crossbar or the forked Y.

Chemically, the end portions vary from antibody to antibody in their protein building blocks or amino acids, and so are termed "hypervariable." This hypervariability in chemical structure, pinpointed by T.T. Wu, Ph.D., and Elvin A. Kabat, Ph.D., at Columbia University in 1970, provides a molecular basis for binding to individual targets, or haptens, to immobilize them. In March of this year, Drs. Padlan and Davies reported that the frequency of amino acid substitutions in various antibodies paralleled their structural variability. In the current report they emphasize the striking similarities between human and rodent antibodies, and also note differences in the depth and width of the cleft in their "business ends."

Drs. Segal, Padlan, and Davies analyzed the structure of the hapten-combining lobes of antibody by several techniques, including X-ray diffraction. Crystals of antibody fragments were bombarded with X-rays, producing diffraction patterns which could be visualized on film. Then heavy metal atoms (which scatter X-rays markedly) were inserted into the crystals to make structural features more discernible. Mathematical data on the spacing and position of the diffraction points were entered into a computer at NIH's Division of Computer Research and Technology. With this technique, the investigators generated topographic maps (electron-density maps) of cross-sections of the hapten-binding antibody lobes. The antibody's short or "light" chains were distinguishable from its longer, "heavy" chains. And the manner in which

(more)

they are inter-twined and folded one upon the other could also be discerned.

The NIH scientists then began construction of a three-dimensional wire model illustrating the structure of the antibody lobes that bind haptens and comparable larger molecules called antigens. The lobes are nicknamed Fabs, for Fragments, antigen-binding.

To assure accuracy the scientists checked the Fab structure frequently against the topographic maps of the X-ray diffraction data. They did this by use of a half-silvered mirror. One side of the mirror reflected the wire model; on the other, the topographic map was projected. Modifications in the placement or alignment of the wire sub-units representing individual amino acids were made whenever indicated.

The resulting three-dimensional model is believed to represent in detail the basic structure of all antibodies. (See illustration on page six)

Dr. Davies noted that the structural analysis would have been impossible without a source of crystallizable antibody. (Most antibodies, produced by a variety of plasma cells, are heterogeneous and won't crystallize.) This critical part of the puzzle was solved with the ingenuity of Michael Potter, M.D., and his NCI colleagues. Dr. Potter provided quantities of the unique, homogeneous antibody produced in plasma cell tumors of inbred mice. Fragments of these antibodies, chiefly from the mouse tumor McPC-603 (McIntire plasmacytoma), are now known to have the same three-dimensional structure as antibody fragments from patients with a related type of cancer, multiple myeloma. This conclusion was dependent in part on information about the amino acid sequence of the McPC-603 antibody which was provided by Dr. Potter and Stuart

(more)

Rudikoff, Ph.D., of NCI.

Dr. Davies and his colleagues also analyzed information on amino acid sequences of other crystallized antibodies and Fab fragments that had been published by the research teams at Johns Hopkins, Argonne National Laboratory, and the Max Planck Institute. Comparing this with NIH information about the mouse antibody fragment of McPC-603, Davies and associates sound all of the amino acid sequences and their relative positions in the antibodies to be remarkably similar, except in regions that bind haptens. The findings were also consistent with amino acid analyses of segments of three other mouse myeloma antibodies that had been described by Drs. Rudikoff and Potter in 1974.

The NIH scientists caution that the conclusions to date are drawn from only a few sources of antibody. And antibody structure was studied in crystalline form, not in the liquid state in which antibodies exist in the human body. (Techniques for the analysis of soluble antibodies have not yet been developed.) Despite these limitations, the NIH scientists consider that the recently acquired information is a major step toward greater understanding of antibodies. They expressed the hope that the knowledge might be useful in improving the body's immune defenses against various diseases.

The potential availability of synthetic antibodies, if they could be manufactured, would have a major impact on medical practice and the prospects for treating many human diseases.

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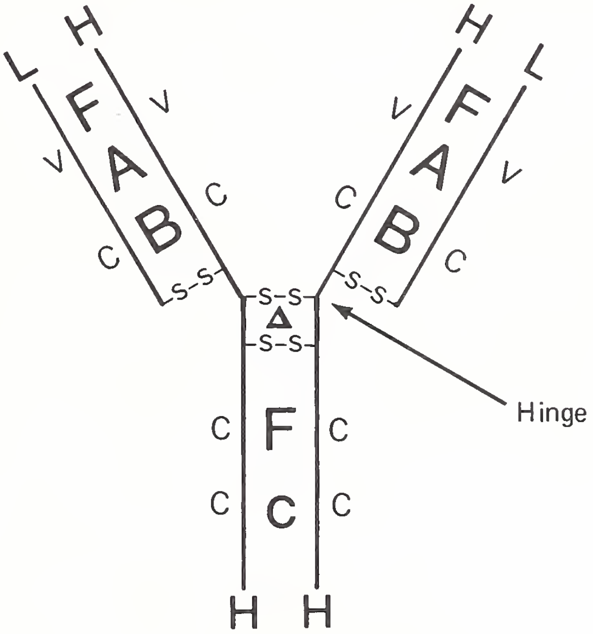
ANTIBODY STRUCTURE



The 3-lobed structure of antibody was first described by Dr. Rodney R. Porter of Oxford University in 1959. The structure consists of 2 Fabs (Fragments, antigen-binding) and an Fc (Fragment, crystalline) segment.

For this research on structure, and evidence of antibody's 4 chains (2 light and 2 heavy chains), Dr. Porter shared a Nobel Prize in 1972 with Dr. Gerald M. Edelman of Rockefeller University.

Key:

Fab = Fragment, antigen binding
Fc = Fragment, crystalline
L = Light chain of antibody
H = Heavy chain of antibody
—S—S— = Interchain disulfide bridge
V = Variable region
C = Constant region

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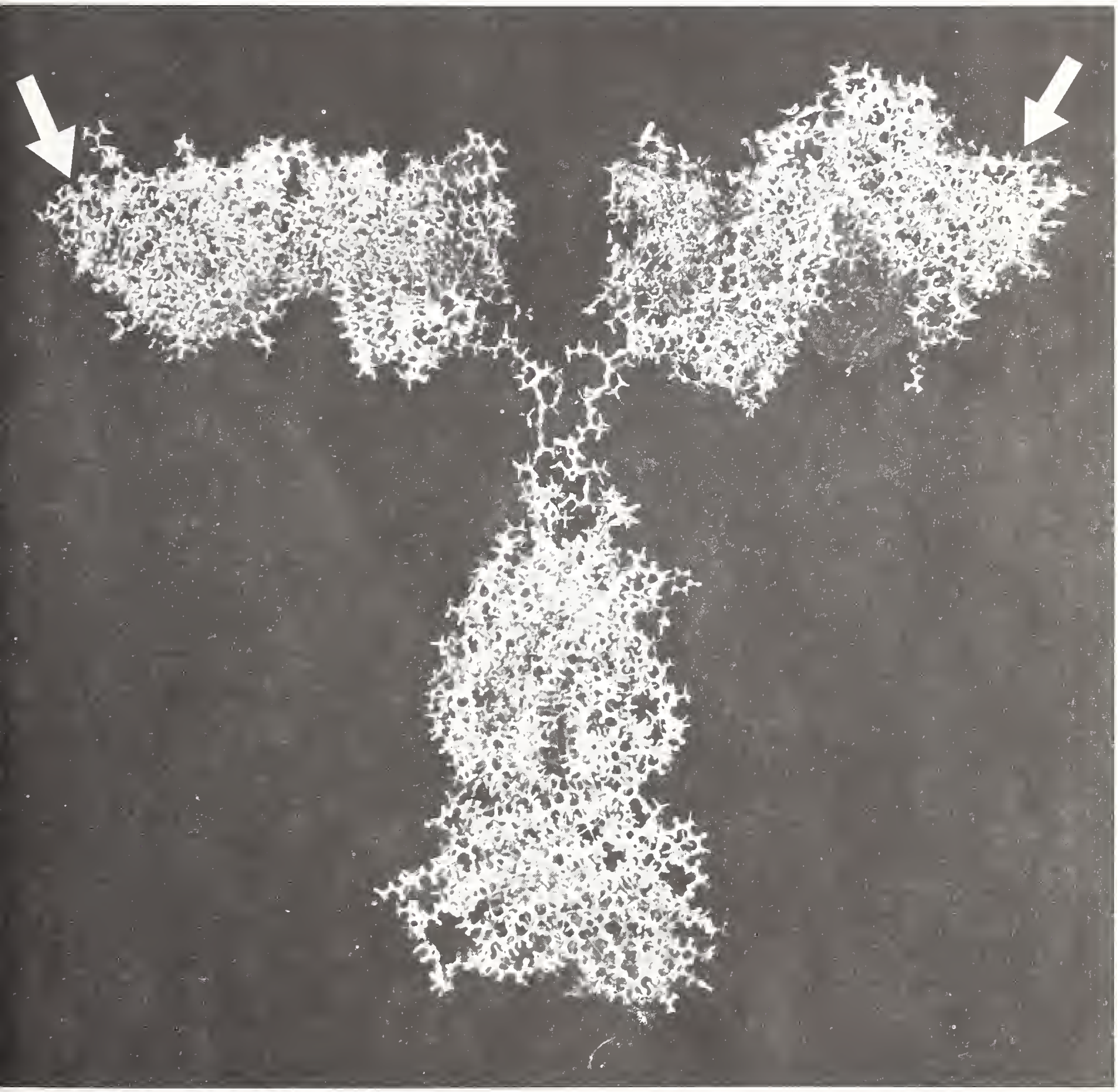
3-DIMENSIONAL STRUCTURE OF ANTIBODY



Arrows show part of antibody where haptens or antigens are trapped.

(more)

Standing in front of his three-dimensional model of the basic structure of an antibody is Dr. David R. Davies of the National Institute of Arthritis, Metabolism, and Digestive Diseases. (NIH Photo #1435-available as a black and white print or a color slide)

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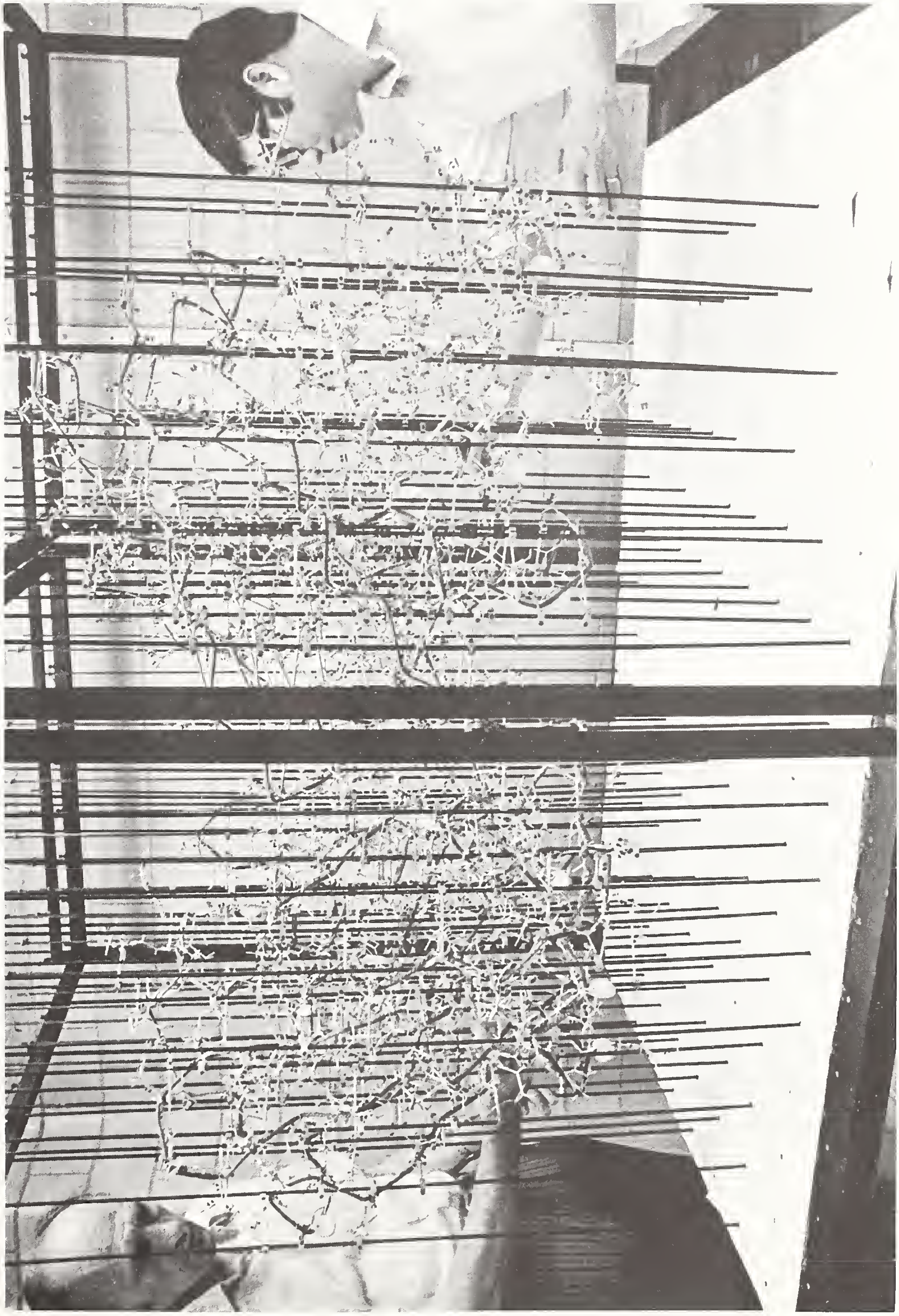
ANTIBODIES (Cont'd)



Dr. David R. Davies (left) and Dr. Eduardo A. Padlan of the National Institute of Arthritis, Metabolism, and Digestive Diseases are shown working on a three-dimensional model which they used in their study of antibodies. (NIH Photo #1436)

#

Research Advances

LUNGS MAY IMMUNIZE THEMSELVES AGAINST SOME PHOTOCHEMICAL SMOG

Respiratory studies on monkeys and rodents at the California Primate Research Center indicate that lungs may be able to immunize themselves against moderate doses of photochemical smog.

The studies reveal that definite biochemical and structural damage takes place in the lungs of monkeys and rodents exposed to 0.2 parts per million (ppm) of ozone for eight hours a day on seven consecutive days. These are typical ambient levels of ozone usually prevalent in parts of California's South Coast Los Angeles Air Basin during the summer months.

However, the lungs in primates and rodents at the Center, which is supported by NIH's Division of Research Resources, seem to adapt and physiologically recover within 90 days. "It is highly likely that similar damage and adaptation can occur in humans," says Dr. Donald L. Dungworth, Ph.D., principal investigator.

Photochemical smog consists of oxides of nitrogen, hydrocarbons, sunlight, and other oxidants. The researchers have found it apparently oxidizes the biological tissues and temporarily impairs the permeability of the membranes in the lungs of the laboratory animals.

Using specially constructed ozone exposure chambers to simulate photochemical smog, the investigators have concluded that adaptation is most successful at 0.5 ppm levels or below. Adaptation by rodents at 0.9 ozone concentration is unsuccessful. At this level, progression worsens rather than

(more)

diminishes.

The mechanism of adaptation and the factors that either prevent or cause lung lesions in monkeys and rodents could also be similar to those occurring in humans.

California's South Coast Basin area experiences some of the highest levels of photochemical smog in the nation. For example, from July 1 to September 30, 1974, oxidant concentration of 0.2 ppm or greater occurred in the eastern portion of the Basin on 84 of the 92 days. A concentration of 0.5 ppm was encountered on 9 of the 92 summer days in 1974; 0.8 ppm is an extremely rare occurrence.

One particular category of people who are affected more by severe smog are those with chronic pulmonary diseases, such as bronchitis, emphysema, and asthma. Such individuals not only have pulmonary insufficiency, but their capacity for adaptation is presumably lessened.

Increased levels of vitamin E intake could possibly be one modifying factor in combating the harmful effects of high smog levels, the scientists have found. Deficiencies of vitamin E in rodents increased the susceptibility of the lungs to damage by ozone during the study. Further vitamin E studies with rhesus and bonnet monkeys are planned at the Center.

The findings in this study on the effect of ambient levels of ozone on the lungs were published in the July 1975 issue of *Federation Proceedings*.

(See photographs on pages 25 and 26)

#

Research Advances

LACK OF ADA ENZYME MAY CAUSE IMMUNODEFICIENCY

A lack of the enzyme, adenosine deaminase (ADA), may be causally related to severe combined immunodeficiency. However, the enzyme deficiency does not interfere with the establishment of normal immunologic function by bone marrow transplants, according to the National Institute of Allergy and Infectious Diseases grantees. The investigators, Drs. Robertson Parkman, Erwin W. Gelfand, Fred S. Rosen, Arnold Sanderson, and Rochelle Hirschorn, are from Harvard Medical School and New York University School of Medicine. Their findings were published in the April 3 issue of *The New England Journal of Medicine.*

Adenosine deaminase (ADA), is a common enzyme that catalyzes the conversion of adenosine to the nucleoside, inosine. Without ADA, adenosine may accumulate and be toxic to cells such as fibroblasts and lymphoid cells. Although ADA has proved to be present in thousands of normal persons, its absence was discovered in several infants with severe combined immunodeficiency. Not all children with this rare inherited and uniformly fatal immunodeficiency lack ADA. However, because these two unusual deficiencies appear in combination, it is believed that they may somehow be related.

Dr. Parkman and his colleagues treated three such children from two families by transplanting bone marrow from histocompatible siblings with normal immunologic function and ADA levels. In two of the three patients, the transplantations were successful, and normal immunologic function was established, but the enzyme deficiency remained. Repeated attempts at transplantation in the third patient were not successful and she died at 19 months of age.

An ADA deficiency does not affect the success of bone marrow transplantation.

(more)

ADA ENZYME (Cont'd)

It does appear to be an inherited trait and related to immunodeficiency. The investigators speculate that the ADA deficiency is a genetic mutation which blocks the development of normal immunocompetent cells in affected fetuses. The blockage may be caused by the accumulation of adenosine or some other reaction. However, once immunocompetence has been established by the transplantation of normal cells, the enzyme deficiency does not seem to affect the patient's well-being.

#

ANTIVIRAL AGENTS--Viral infections are the most common of those affecting the public and a number of drugs and other antiviral substances are under investigation by the National Institute of Allergy and Infectious Diseases for possible use in treatment. One of these substances, called interferon, is a protein produced by body cells in response to invasion by an infectious agent. Scientists are studying the effects of above-normal amounts of interferon on viral infections. They are also developing ways to produce interferon outside the body or to increase the body's production without toxic side effects.

#

August 25, 1975

Research Advances

ORAL ZINC SULFATE THERAPY RAPIDLY HELPS ONE PATIENT

Colorado scientists have described a rapid and dramatic clinical response to oral zinc sulfate therapy in a patient with acrodermatitis enteropathica, a potentially fatal gastrointestinal and cutaneous disorder.

Acrodermatitis enteropathica, which begins in infancy, has been treated since 1953 successfully, but empirically, by oral administration of di-iodohydroxyquin or related compounds. Large doses of these agents are required continuously, however, and such therapy is not entirely satisfactory.

Several investigators have recently reported some success in treating this disorder with oral zinc sulfate. The present case concerns a 22-year-old woman, maintained on di-iodohydroxyquin therapy for 20 years, who responded to oral zinc sulfate with a rapid and complete clinical remission. The findings are compatible with a severe zinc deficiency state, and indicate that the inherited defect in this disease is either in or closely-related to zinc metabolism.

At age one (in 1953) the patient had responded rapidly to di-iodohydroxyquin therapy with a complete remission, but since then had required the drug at the rate of 650 mg three to four times daily. The therapeutic effect of orally-administered zinc sulfate was evaluated over a period of 16 weeks, during which time the patient was alternately on di-iodohydroxyquin or zinc sulfate therapy, or without therapy.

When she was off therapy and in clinical relapse the plasma zinc concentration, serum alkaline phosphatase, and urine zinc excretion rate were extremely

(more)

THERAPY (Cont'd)

low. Di-iodohydroxyquin therapy was accompained by a modest increase in plasma zinc concentration. Oral zinc sulfate (220 mg three times a day, or 50 mg twice a day)resulted in rapid and complete clinical remission, and in a return of plasma zinc, serum alkaline phosphatase, and urinary zinc excretion to normal.

The beneficial effects of zinc therapy in this patient provide further confirmation of the efficacy of oral zinc in the treatment of acrodermatitis enteropathica. It is suggested that further research may reveal a defect in gastrointestinal absorption of zinc, rather than excessive loss of this essential trace element, in affected individuals.

Kenneth H. Nelder, M.D., and K. Michael Hambidge, M.D., of the University of Colorado reported their findings in the *New England Journal of Medicine*, May 15, 1975. Dr. Hambidge is a grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases.

#

CHOLESTEROL--Elevated blood levels of cholesterol and other fatty substances (collectively called lipids) are often strongly associated with increased risk of premature arteriosclerosis and coronary heart disease, according to the National Institutes of Health.

#

Photo Feature

NEW INSTRUMENT LETS SCIENTISTS MONITOR SINGLE CELL ACTIVITY IN THE HUMAN BRAIN

A team of NIH researchers, including neurosurgeons, neurophysiologists, mechanical and electrical engineers, and precision instrument makers, has combined its talents, skills, and knowledge over the past three and a half years to develop techniques for discovering the roles of individual nerve cells in the seizures characteristic of severe epilepsy.

While laboratory researchers have begun to understand fundamental mechanisms of the brain and of epilepsy through animal models and tests, neurosurgeons and neurophysiologists have long sought a reliable and convenient technique for monitoring the minute electrical voltages produced by single nerve cells in the human cerebral cortex, for instance during surgery to remove tissue thought to be causing epileptic seizures.

Since the surface of the brain pulses up to two millimeters with respiration and blood flow when the overlying skull is removed exposing the cortex, special techniques are required for recording from nerve cells near the surface in a manner delicate enough to be used on human subjects in the study and treatment of epilepsy.

To accomplish this, a new instrument called a gas bearing floating microdrive was developed at NIH at the initiative of Dr. Karl Frank, former Chief of the Laboratory of Neural Control, National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), with the support of the Laboratory of Neural Control (LNLC), and the Surgical Neurology Branch of NINCDS, and the Biomedical Engineering and Instrumentation Branch (BEIB), Division of Research Services (DRS). The instrument was designed by Dr. Seth Goldstein of BEIB,

(more)

a mechanical engineer, with the assistance of electrical engineers Dr. Edward Schmidt and Martin Bak of LNLC. Frank Bierley of BEIB performed the precision machining of the instrument.

The microdrive is supported by a fixture clamped to the skull, and operates by causing the recording microelectrode to follow the motions of the brain surface thus remaining close to a single nerve cell. A four-millimeter diameter "rider" follows the movement of the brain by contacting the cerebral cortex with a force of only 0.1 gram and is supported without friction in gas journal bearings by a film of nitrogen gas 0.001 inch thick. A present regulator within the microdrive automatically maintains this minimal contact force level for any electrode insertion angle between 0° and 45° from vertical.

The tungsten wire microelectrode is attached to the rider and protrudes beyond it into the cortex a variable depth controlled by a miniature lead screw having 160 threads per inch. The lead screw is attached to the rider and is rotated without interfering with the brain's motion by an additional, unique system of gas thrust bearings for which NIH recently received a patent in Dr. Goldstein's name.

After several months of trial use of the device with rhesus monkeys, the new microdrive was successfully used on March 9, 1975, to record stable extracellular electrical activity from single cells of the human cortex. The duration of monitoring a single cell was limited only by the time allotted for recording during operating procedure.

The recording was performed in the NIH Surgical Neurology operating suite during a neurosurgical procedure performed by Dr. John M. Van Buren, Chief of

(more)

the Surgical Neurology Branch, NINCDS, to remove an area of scarred cerebral cortex believed to be causing the patient's epilepsy for which medical treatment had proved ineffective.

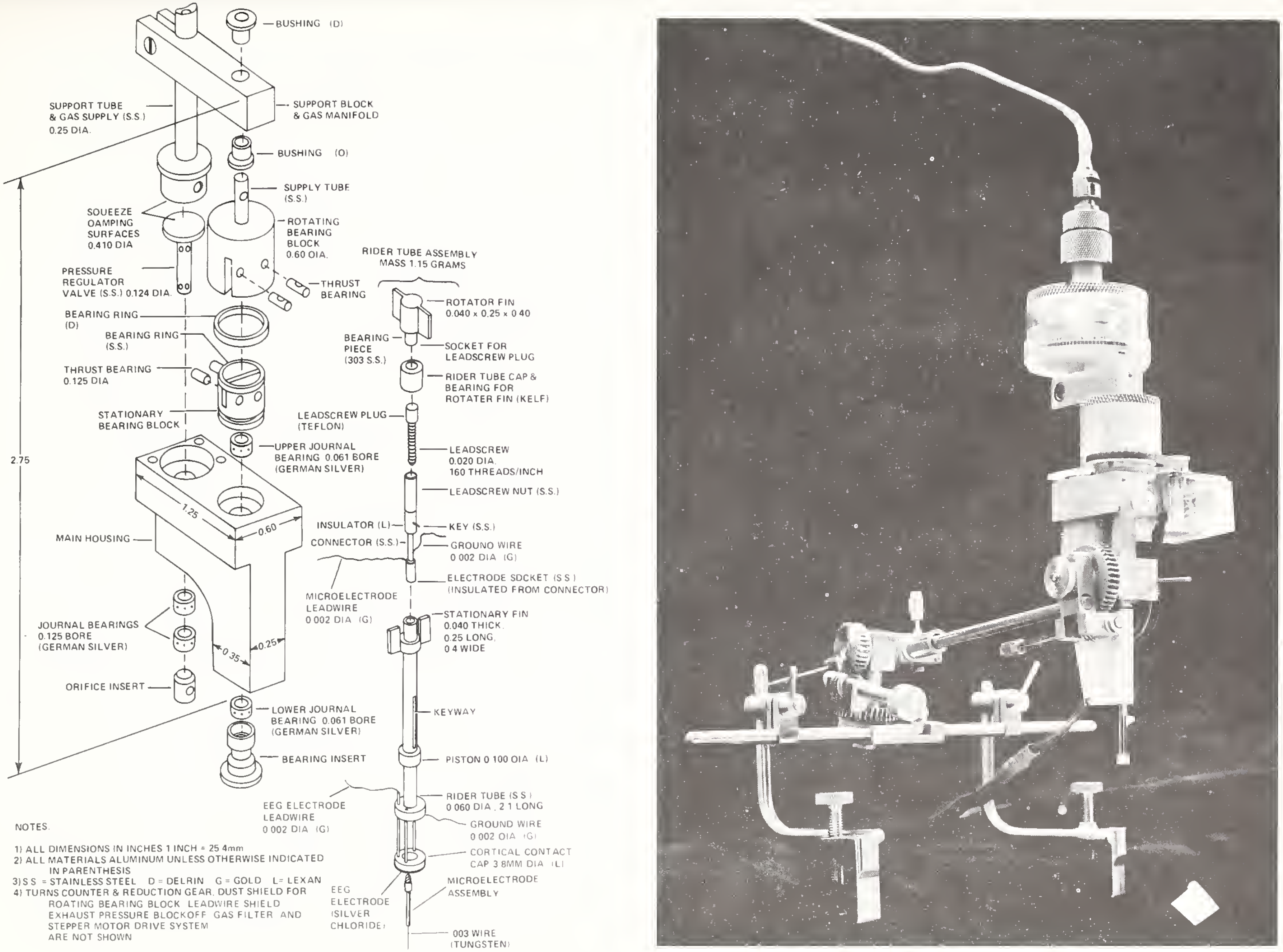
Drs. Schmidt and Goldstein and Mr. Bak managed the electronic recording apparatus and technical aspects of the device,which is linked to oscilloscopes and closed circuit TV for continuous monitoring of cellular activity individually or synchronized with an electroencephalogram obtained from an electrode mounted on the rider.

Dr. John C. Oakley, clinical associate, Surgical Neurology Branch, NINCDS, performed the cortical search for single units, adjusting the microelectrode depth in increments as small as two and a half microns, using the remotely controlled miniature stepper motor mounted on the microdrive. Recording was carried out in an area involved in the epileptic process as determined by electro-corticography performed by Dr. Cosimo Ajmone-Marsan, Chief of the Electroencephalography and Clinical Neurophysiology Branch, NINCDS.

Although the first problem to be attacked with the new techniques made possible with this device will be the role of individual nerve cells in the generation of epileptic seizures, other problems that can be investigated include the role of individual nerve cells in the control of movement, in speech, in vision, in hearing, and in many other normal and abnormal functions of the brain. In preliminary tests intracellular recordings of up to 15 minutes duration have been obtained in Rhesus monkeys using glass micropipette electrodes. A complete set of drawings for the system can be obtained by contacting Dr. Goldstein at BEIB, DRS, NIH, Bethesda, Maryland 20014.

(more)

BRAIN (Cont'd)


BUSHING (D)
SUPPORT TUBE & GAS SUPPLY (S.S.) 0.25 DIA.
SUPPORT BLOCK & GAS MANIFOLD
BUSHING (O)
SUPPLY TUBE (S.S.)
SOUEEZE OAMPING SURFACES 0.410 DIA
ROTATING BEARING BLOCK 0.60 OIA.
PRESSURE REGULATOR VALVE (S.S.) 0.124 DIA.
THRUST BEARING
RIDER TUBE ASSEMBLY MASS 1.15 GRAMS
ROTATOR FIN 0.040 x 0.25 x 0.40
BEARING RING (D)
BEARING RING (S.S.)
BEARING PIECE (303 S.S.)
SOCKET FOR LEADSCREW PLUG
THRUST BEARING 0.125 DIA
RIDER TUBE CAP & BEARING FOR ROTATER FIN (KELF)
STATIONARY BEARING BLOCK
LEADSCREW PLUG (TEFLON)
UPPER JOURNAL BEARING 0.061 BORE (GERMAN SILVER)
LEADSCREW 0.020 DIA. 160 THREADS/INCH
2.75
LEADSCREW NUT (S.S.)
1.25
0.60
MAIN HOUSING
INSULATOR (L)
KEY (S.S.)
CONNECTOR (S.S.)
GROUNO WIRE 0 002 DIA (G)
ELECTRODE SOCKET (S.S.) (INSULATED FROM CONNECTOR)
MICROELECTRODE LEADWIRE 0 002 DIA (G)
STATIONARY FIN 0.040 THICK, 0.25 LONG, 0.4 WIDE
JOURNAL BEARINGS 0.125 BORE (GERMAN SILVER)
0.35
0.25
ORIFICE INSERT
LOWER JOURNAL BEARING 0.061 BORE (GERMAN SILVER)
KEYWAY
BEARING INSERT
PISTON 0 100 OIA (L)
RIDER TUBE (S.S.) 0 060 DIA, 2 1 LONG
EEG ELECTRODE LEADWIRE 0 002 DIA (G)
GROUND WIRE 0 002 OIA (G)
NOTES.
1) ALL DIMENSIONS IN INCHES 1 INCH = 25 4mm
2) ALL MATERIALS ALUMINUM UNLESS OTHERWISE INDICATED IN PARENTHESIS
3) S.S = STAINLESS STEEL D = DELRIN G = GOLD L = LEXAN
4) TURNS COUNTER & REDUCTION GEAR, DUST SHIELD FOR ROATING BEARING BLOCK LEADWIRE SHIELD EXHAUST PRESSURE BLOCKOFF GAS FILTER AND STEPPER MOTOR DRIVE SYSTEM ARE NOT SHOWN
CORTICAL CONTACT CAP 3 8MM DIA (L)
EEG ELECTRODE (SILVER CHLORIDE)
MICROELECTRODE ASSEMBLY
003 WIRE (TUNGSTEN)

Here are a diagram and a photograph of the gas bearing floating microdrive that was developed and used clinically at the National Institutes of Health. (NIH Photos #1437 and #1438)

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NEWS & FEATURES From NIH August 25, 1975

Photo Feature

NCI STUDIES SIGNIFICANCE OF PRESENCE OF AFP IN BLOOD

A substance that is normally present in the blood of fetuses may reappear in adults with certain types of cancer and can be used to detect the presence of those cancers.

The significance of the presence of the substance, alpha-fetoprotein (AFP), and of its changes during the course of cancer therapy was explained by Thomas A. Waldmann, M.D., Chief of the National Cancer Institute Metabolism Branch, at the National Conference on Advances in Cancer Management in Denver, on May 2, 1975. The meeting was cosponsored by the National Cancer Institute and the American Cancer Society.

The level of AFP was elevated by as much as 1,000 to 100,000 times the normal level in the serum of about 75 percent of patients who had hepatoma (liver cancer) or certain cancers of the testes (male reproductive glands), Dr. Waldmann said. Elevated AFP was also detected in 22 percent of patients with pancreatic cancer, 18 percent of patients with stomach cancer and in some patients with lung cancer and cancer of the colon. It is these organs in the fetus, and the tissue from which they are derived in the embryo, that produce AFP.

Production of AFP decreases after birth, and the level of AFP in the serum of a healthy adult is less than 40 nanograms per milliliter (a nanogram is one billionth of a gram). The increased production of AFP in cancer patients may be an indication of increased numbers of fetus-like cells in the affected organ.

(more)

AFP (Cont'd)

Scientists have developed the means only recently to detect AFP in concentrations as low as 40 nanograms per milliliter (one part in 25 million). Previous methods allowed them to detect concentrations only as low as 10,000 nanograms per milliliter (one part in 100,000). The technique that is now used, called double antibody radioimmunoassay, is sensitive to five nanograms per milliliter of serum, or one part in 200 million.

A second fetal protein, the beta chain of human chorionic gonadotropin (HCG), has been used with AFP as an indicator of the presence of cancer. In testicular tumors, for example, Dr. Waldmann found that AFP was elevated in 75 percent of the patients and HCG was elevated 66 percent. However, individual patients did not always show an elevation in both indicators. One or the other of the indicators was elevated in 90 percent of patients with testicular tumors.

In addition to serving as a means to detect cancer, AFP may also be used to monitor the progress of therapy. Dr. Waldmann cited a study of 13 patients at NCI, each of whom had elevated levels of both AFP and HCG and was diagnosed as having testicular teratocarcinoma. After treatment with anticancer drugs began, the levels of the indicators began to drop in 12 of the patients who responded to treatment. Levels remained elevated in the one patient whose cancer was not affected by treatment.

In one of the patients who responded, both indicators fell to normal levels. The patient has not had any indication of a recurrence of cancer after more than two years. In the other 11 patients, the levels of both indicators dropped steadily. One indicator, AFP in some patients and HCG in others, eventually returned to a normal level in nine of the patients.

(more)

The other indicator remained slightly elevated in these nine patients, although clinical evidence of cancer could not be detected in five of them.

In the nine patients, including the five without clinical evidence of disease in the initial period following chemotherapy, the indicator that had remained slightly elevated during therapy climbed to a very high level after treatment stopped. Within two to twelve months after the level of indicator increased, the tumor recurred.

The fact that only one indicator returned to a normal level and remained at that level even after tumor recurrence indicates that AFP and HCG may be produced by different cells, Dr. Waldmann said. The testicular cancers in which AFP and HCG are found are quite complicated, comprising a number of different cell types. The therapy the patient undergoes may be completely effective against one type of cell, causing a drop to normal levels of the indicator secreted by that cell. However, the presence of minute, though elevated, levels of the other indicator, Dr. Waldmann believes, may be evidence that a few cancer cells have survived the therapy. When treatment is stopped, the surviving cells proliferate into another tumor. The amount of indicator in the serum of these patients will be elevated long before a tumor is clinically evident.

The concentrations of HCG and AFP in any testicular cancer patient could be correlated with the size of the tumor and the progress of therapy in only that patient, Dr. Waldmann added. Some patients with small tumors had a marked elevation of the indicators, whereas other patients with larger tumors had only a slight elevation. Thus, a general statement cannot be made that the presence of a specific amount of the indicators correlates with a tumor of any given size in all patients.

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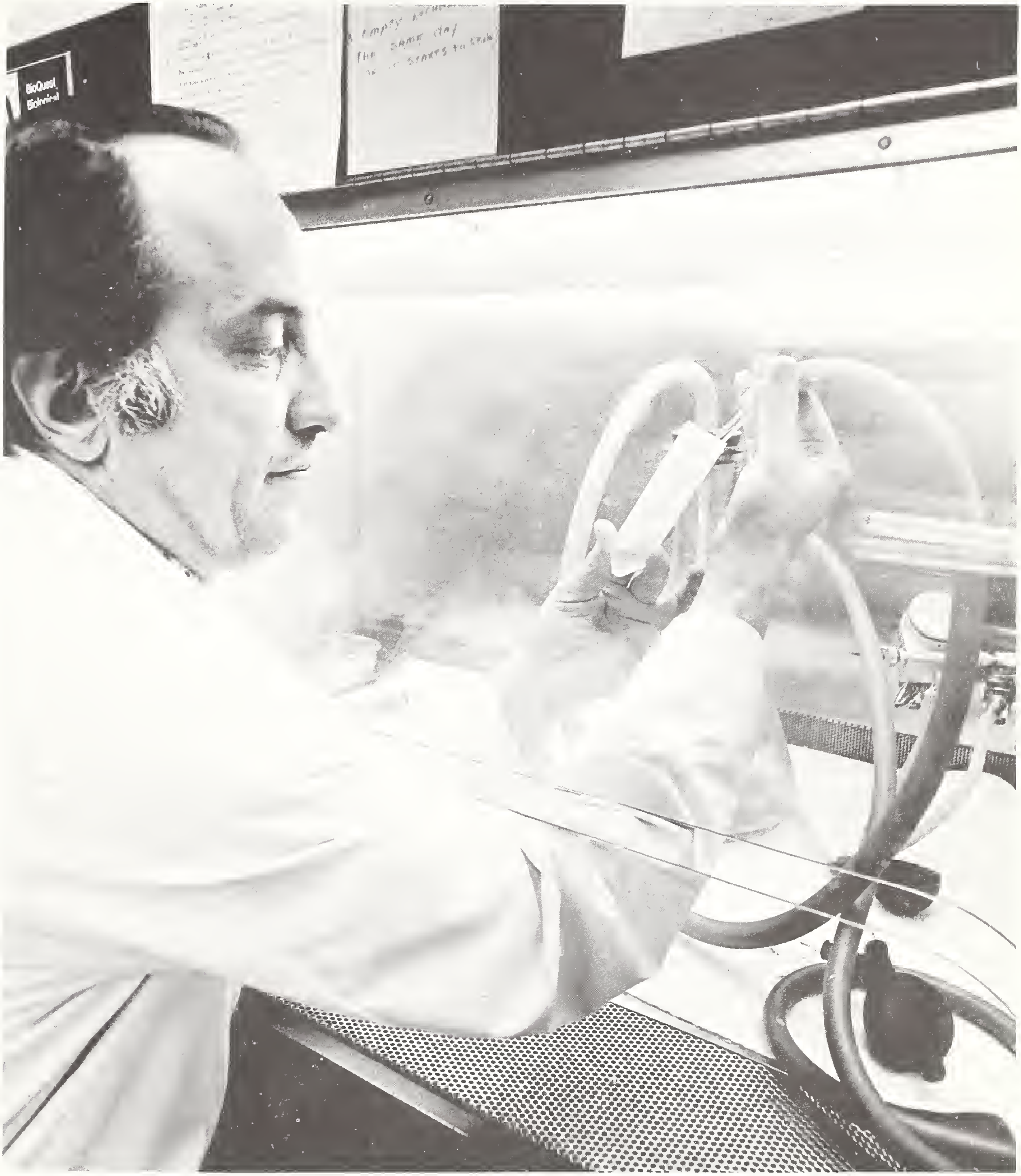
AFP (Cont'd)



Working in his laboratory at the National Cancer Institute, Thomas A. Waldmann, M.D., is studying the significance of the presence of alpha-fetoprotein in the blood. Dr. Waldmann heads the National Cancer Institute's Metabolism Branch. (NIH Photo #1439)

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NEWS & FEATURES From NIH August 25, 1975

News Feature

FELLOWSHIPS AVAILABLE IN SWEDEN AND SWITZERLAND

The Fogarty International Center (FIC), of NIH, has announced that the Swedish Medical Research Council and the Swiss National Science Foundation will each make available, in 1976, three research fellowships to qualified biomedical scientists. These fellowships will provide postdoctoral training in basic or clinical areas of medical research.

To be eligible candidates must be American citizens who have been engaged in independent responsible research in one of the health sciences for at least two of the past four years. They must present evidence of aptitude and promise in basic sciences or clinical research, with an active interest in pursuing a research career in a health science field. Applicants must also provide evidence of acceptance by a training institution and preceptor. It is the applicant's responsibility to arrange for his research training with the preceptor and to present in his application a complete and explicit plan for research training. Affiliation with the preceptor is documented in the Facilities and Commitment Statement which must accompany each application.

The fellowship must be started within ten months of the date of its award, as set by mutual agreement of the applicant and the institution. Fellowships will normally extend for 12 months.

The fellowships provide for reimbursement of the cost of round trip tourist air fare tickets for the Fellow and his family. Health insurance is provided during the term of the fellowship. Stipends for the Swedish Medical Research Council Fellowships range from $10,000 to $13,600 per year, depending upon the number of years of postdoctoral research experience at the time of

(more)

FELLOWSHIPS (Cont'd)

award. The Swiss National Science Foundation stipends range from 24,288 Swiss francs ($9,533) to 30,624 Swiss francs ($11,627) depending upon the age of the applicant at the time of award. In addition, the Swiss National Science Foundation Fellowships provide 3,960 Swiss francs ($1,560) for the spouse and 1,200 Swiss francs ($470) for each child.

Application materials may be obtained from Dr. Eugene L. Walter, Jr., Fogarty International Center, NIH, Bethesda, Maryland 20014. The deadline for receipt by NIH of completed applications is January 1, 1976. Applications will be reviewed for appropriateness and scientific merit at the Fogarty International Center. They will be forwarded to Sweden or Switzerland, as appropriate, for final selection and award in late Spring 1976.

All correspondence with FIC concerning these fellowships must be clearly marked as either "Swedish Medical Research Council Fellowship" or "Swiss National Science Foundation Fellowship."

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DENTAL PLAQUE--Dental plaque is a colorless, transparent film on the teeth made up of saliva and bacteria materials. The National Institutes of Health reports that plaque contributes to tooth decay, and is also an agent in the cause and development of periodontal disease.

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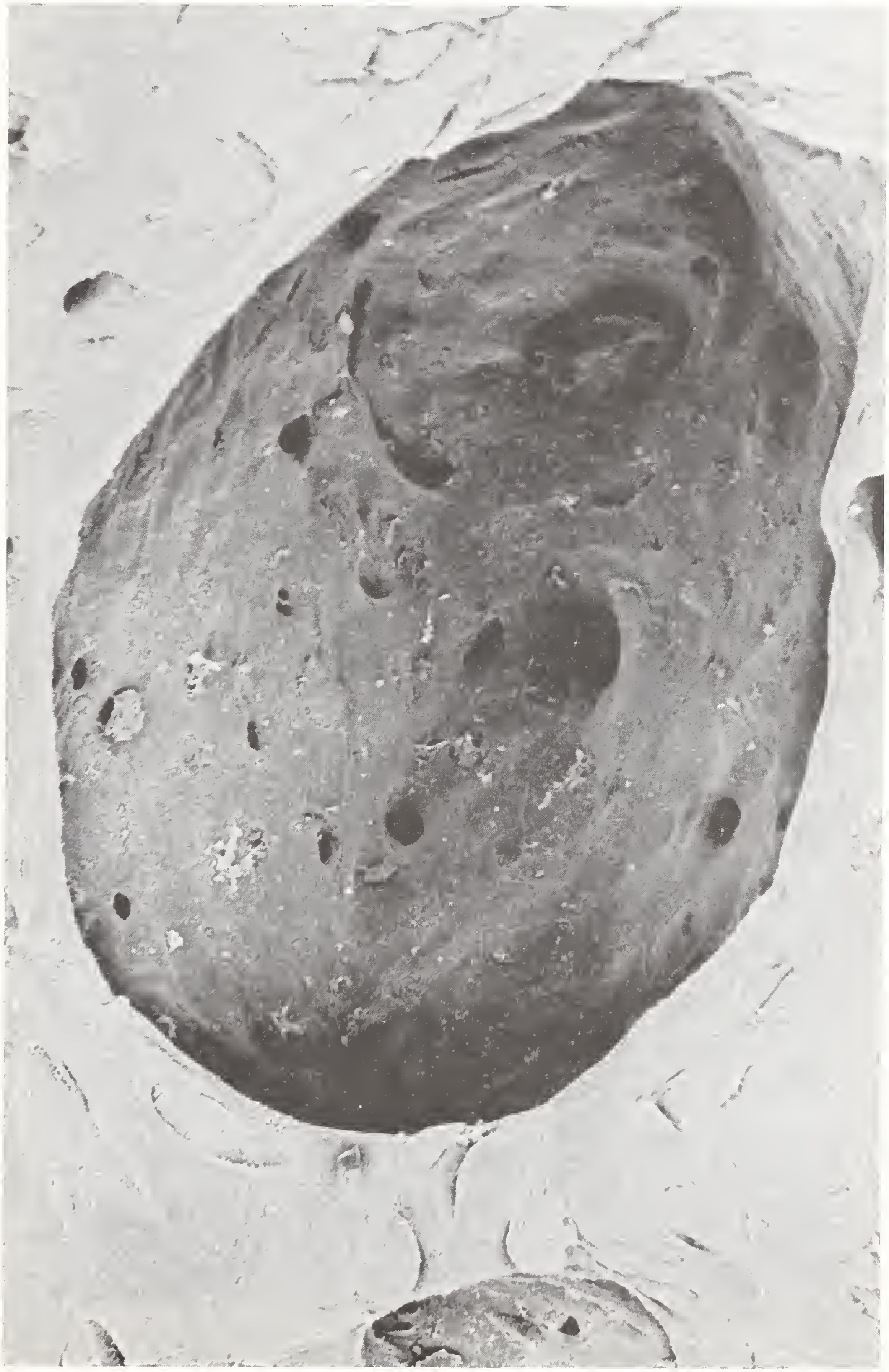
Research Illustrated

CONTRASTING VIEWS OF MONKEY LUNGS, CORONARY ARTERIES, MOUSE LENSES



A scanning electron micrograph from the California Primate Research Center, Davis, shows a section of the respiratory bronchiole in a normal rhesus lung. As the smallest airways in the lung, these outpouchings are prime targets for the damaging effects of oxidant air pollutants. The Center is supported by the NIH Division of Research Resources. (NIH Photo #1440)

(See story on pages nine and ten)

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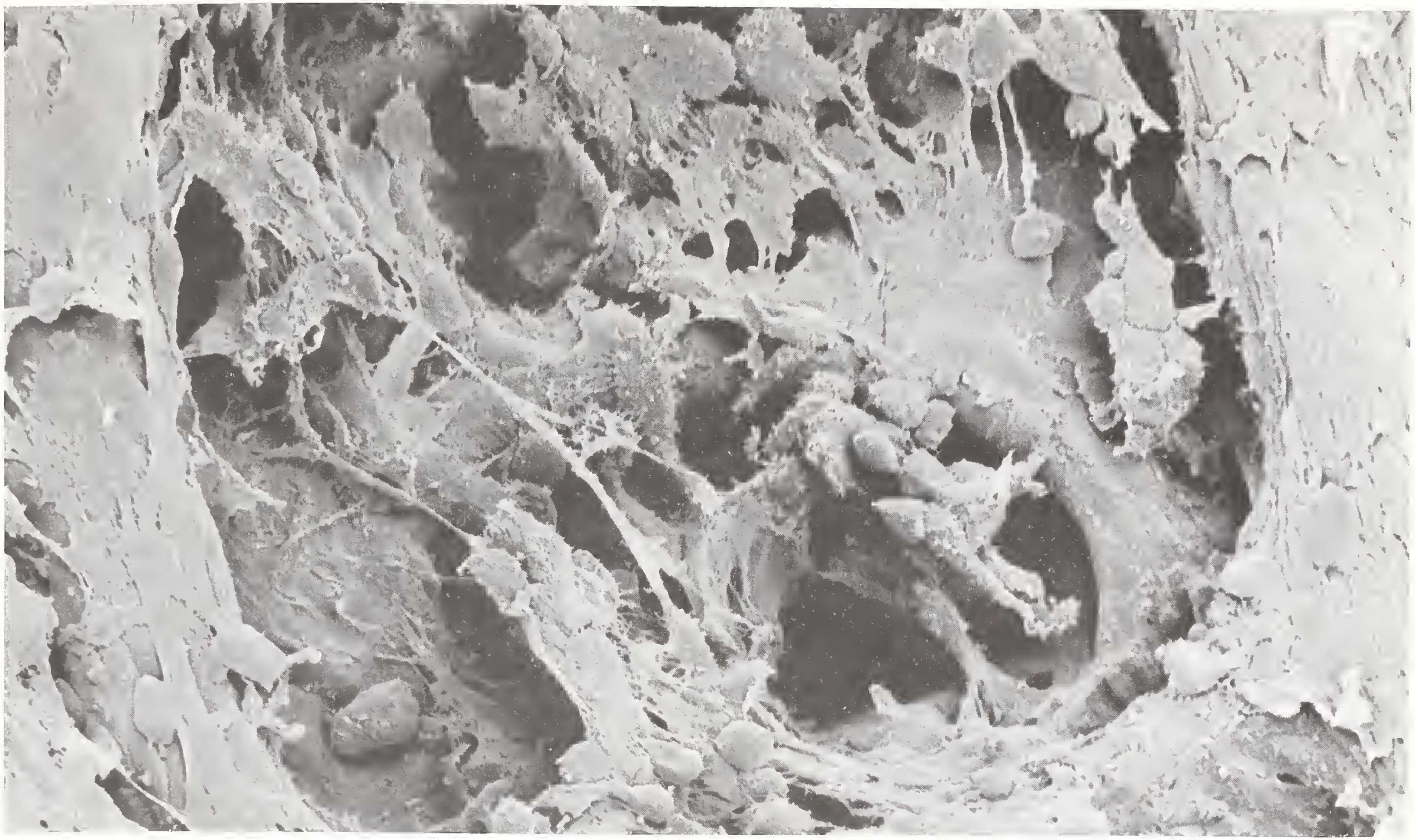

This scanning electron micrograph shows the alveolus from a respiratory bronchiole of a rhesus monkey exposed to 0.5 ppm of ozone, eight hours a days for seven consecutive days. A large number of inflammatory cells and amorphous debris fill the alveolus and coat the airway surface. Immune defenses in the body will rectify this condition within 90 days despite continued exposure to lower photochemical smog levels, California Primate Research Center scientists have found. The Center is funded by the NIH Division of Research Resources. (NIH Photo #1441)

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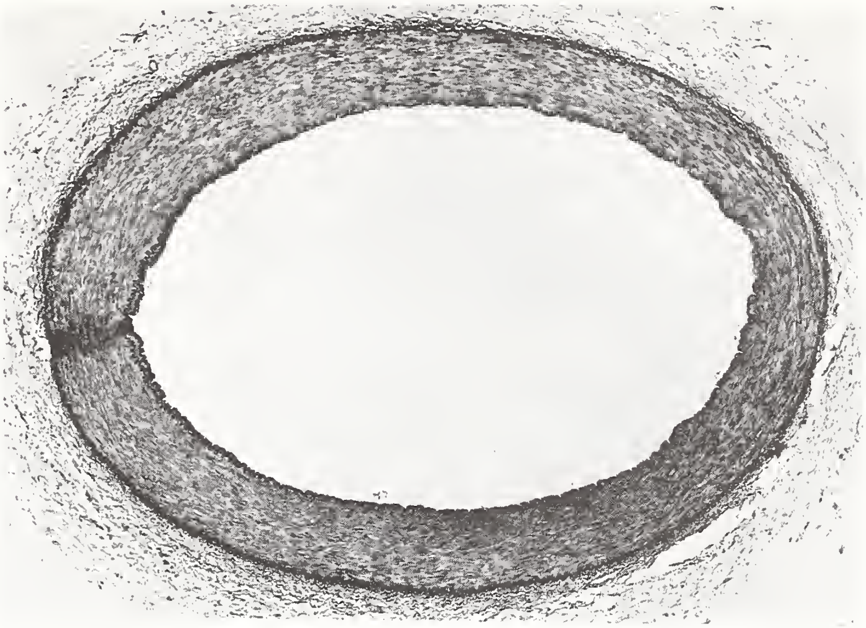
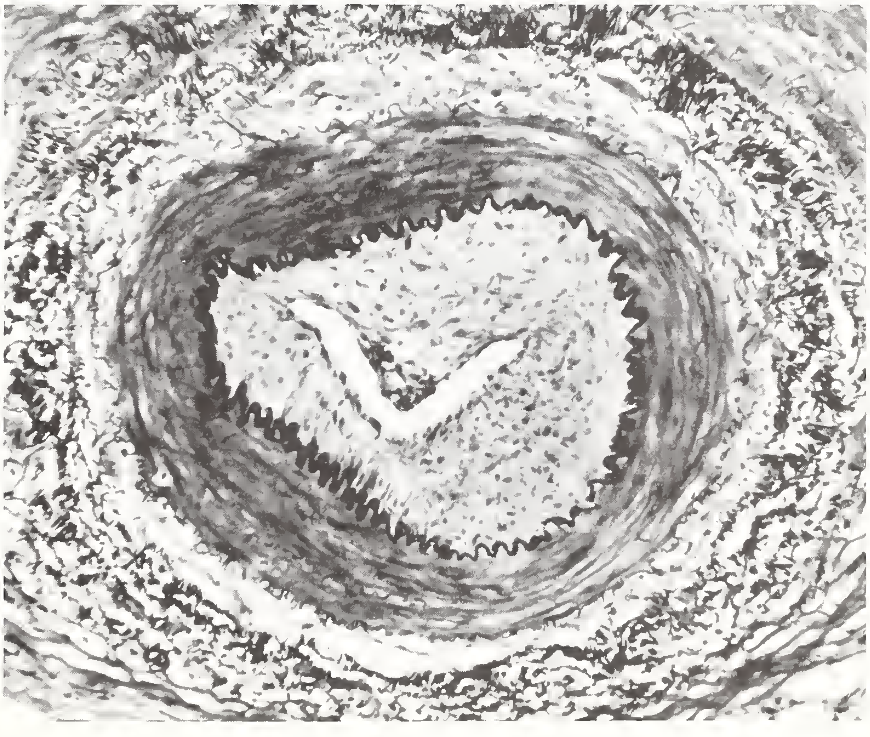


When a normal coronary artery (above) is nearly blocked by fatty deposits (below), this is a characteristic of atherosclerosis. This condition is one of several that are under intensive investigation by the National Heart and Lung Institute. (NIH Photo #1442 and #1443)



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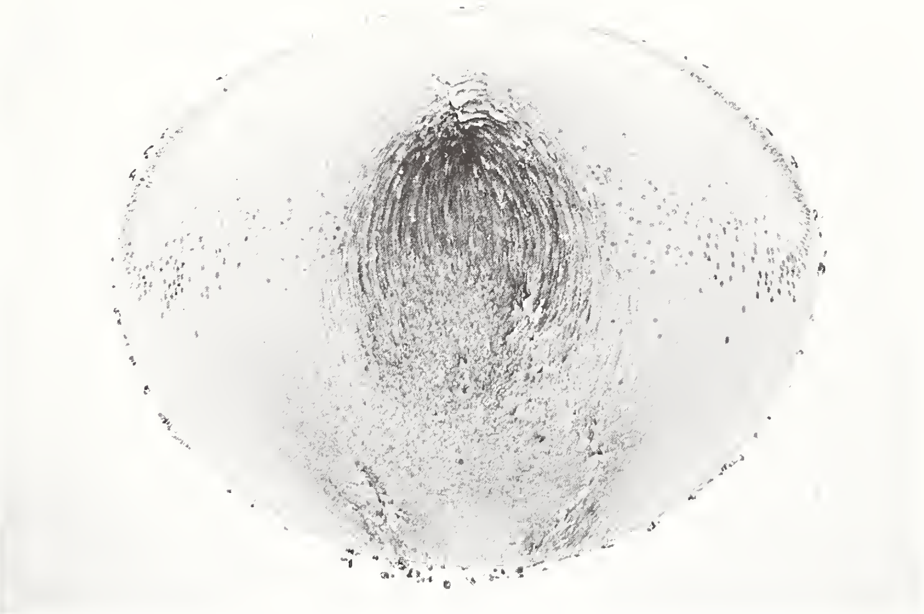
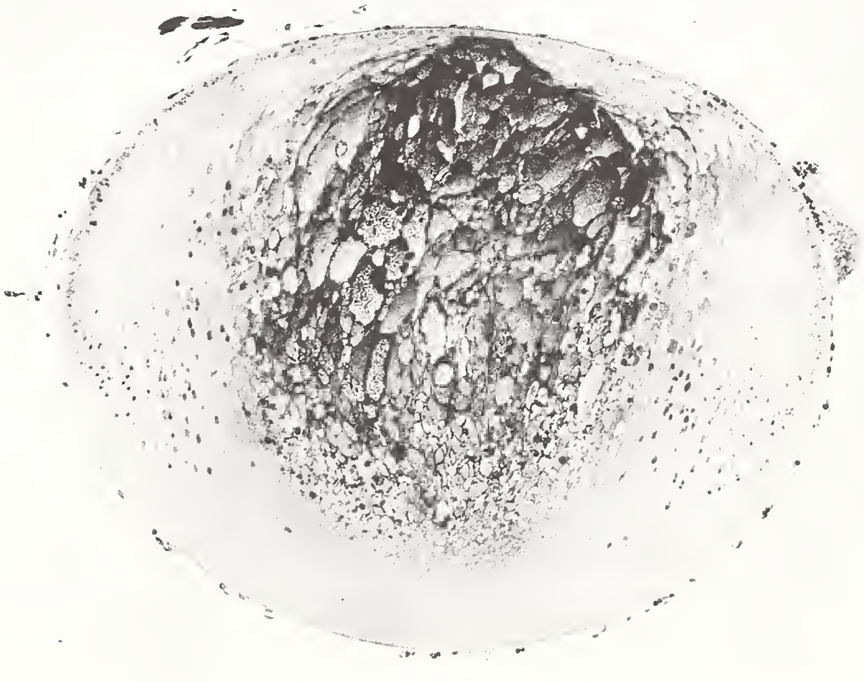
VIEWS (Cont'd)



The National Eye Institute is seeking ways to solve the cataract problem, a leading cause of blindness in the United States. Animal studies include one in which a normal, 18-day embryonic mouse lens (above) is contrasted with a Fraser, 18-day embryonic mouse cataract (below). (NIH Photo #1444 and #1445)



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Disease Profile

PROLONGED TORSION DYSTONIA CAN LEAD TO DISTORTED POSTURE

Torsion dystonia, or dystonia musculorum deformans, is a prolonged and often incapacitating neurological disorder causing bizarre involuntary movements in its victim's arms, legs, head, and torso. If these movements continue over an extended period of time, they can produce distorted posture.

Prior to 1966 many physicians believed that torsion dystonia was not an organic disorder but rather a functional disorder with a neurotic or hysterical basis for the abnormal movements. That year, findings of NINCDS scientists indicated that torsion dystonia was indeed of organic origin. In addition, they were able to identify two hereditary forms. It is now known that there is also an acquired form.

The "recessively inherited" form occurs in about one-fourth of the offspring of parents who carry but do not express the defective gene. The disorder affects primarily people of Eastern European Jewish ancestry. About one out of every 100 Americans of this origin carries the dystonia gene, a frequency only slightly less than the frequency of Tay-Sachs disease. However, because Tay-Sachs disease leads to early death and dystonia usually does not, there are more living patients suffering from dystonia than from Tay-Sachs disease.

The "dominantly inherited" form of dystonia is passed from a parent who usually is affected with the disorder. In one of the many such families under study by NINCDS, there are at least 13 affected in four generations.

"Acquired dystonia" can result from environmental causes such as head

(more)

DYSTONIA (Cont'd)

injury at birth, infection, and even certain drugs. There are thousands of patients with this type. Dystonic movements also occur in many patients with other neurologic disorders, including some patients with Parkinson's disease receiving L-Dopa therapy.

At the NINCDS, where a registry of hereditary dystonia cases is maintained, 180 affected families involving approximately 500 cases have been evaluated. Many more cases are known but have not been studied. In addition, a special kind of dystonia localized to the neck is relatively common. This condition, which is called torticollis, produces a twisting of the neck and an unnatural position of the head.

At present, NIH research directly devoted to this rare disease includes genetic and epidemiological studies. A substantial amount of basic, non-categorical research in physiology, biochemistry, and other disciplines is also of potential relevance to dystonia.

The cause of dystonia remains unknown, but many scientists believe the problem originates in an area of the brain called the basal ganglia.

In recent studies, NINCDS scientists, collaborating with others, uncovered what appears to be a biochemical defect in one form of dystonia involving the elevation of a particular enzyme in the blood of these patients. If this finding is confirmed, it may lead to a better understanding of the nature of these disorders and help to identify victims whose symptoms have not yet appeared. Such a diagnostic tool would be a valuable aid to physicians providing genetic and family counseling.

(more)

DYSTONIA (Cont'd)

As yet there is no established treatment for the underlying disorder, but dystonic symptoms can sometimes be controlled by drugs such as diazepam (Valium) which relaxes the muscles. Another drug, L-Dopa, which can cause dystonic symptoms in some Parkinson patients, ironically can help alleviate symptoms in some patients with dystonia. Fortunately the search for effective drugs is becoming much more active.

During 1974 scientists at Mount Sinai Hospital, New York, reported that they have been able to treat dystonia patients successfully with carbamazapine (Tegretol), a drug recently made available for general use following extensive NINCDS-sponsored studies. Several dozen patients with both acquired and hereditary forms who were treated with the drug have had sustained improvement for periods up to one year,according to the scientists.

Advanced dystonia may be helped by surgery on a structure deep within the brain called the thalamus which influences the body's pattern of movements. Most persons undergoing this operation have been helped at least temporarily. NINCDS scientists are continuing their efforts to improve surgical treatment and to develop more effective drugs.

In 1970, NINCDS sponsored a conference on dystonia at which important information regarding the clinical, genetic, pathological, biochemical, and therapeutic aspects were discussed and later published for use by the medical and scientific community. Because of the resulting increase in scientific interest an International Symposium on Dystonia was held in May 1975.

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News Releases Issued

MONKEY MALARIA--NIH scientists have identified, for the first time, a genetic factor which prevents the invasion of human red blood cells by a monkey malaria parasite. As reported in the August 15, 1975, issue of *Science*, the unusual worldwide distribution of this factor--the Duffy negative red blood cell genotype--suggests that it may also be protecting certain human populations against one species of malaria.

Three Duffy genes determine the presence or absence of Duffy a or b antigens on the surface of human red blood cells. The Duffy negative genotype--indicated by the failure of blood cells to react with antibodies to Duffy a or b antigens--is found in 90 percent of West Africans and 65 percent of American blacks--groups known to be resistant to infection by the human malaria parasite, *Plasmodium vivax*. This gentoype is extremely rare in racial groups susceptible to *P. vivax*.

This association between genotype and susceptibility suggests that Duffy antigens a and b may be the receptors on red blood cells which allow invasion by *P. vivax*. However, confirmation of this relationship must await analysis of these antigens in Africans found to be infected with *P. vivax*.

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DUST EXPOSURE--Analysis of representative samples of spackling, patching, and taping compounds by grantees of the National Institute of Environmental Health Sciences has shown that some contain asbestos minerals as well as other potentially-harmful substances. Measurements suggest that home repair or construction work involving use of such materials may result in exposure to dust at concentra-

(more)

tions sufficient to produce disease. Details of these findings appeared in the August 15, 1975, issue of *Science*.

Workers exposed to asbestos have been shown to face a greatly-increased risk of developing lung cancer, mesothelioma (a rare form of cancer), cancers of the gastrointestinal tract, and asbestosis (a scarring of the lungs). These effects do not show up until two or three--or sometimes even four--decades after the first exposure to asbestos. The results of these studies have been made available to the Occupational Safety and Health Administration and to the Consumer Product Safety Commission.

- - -

TOOTH TERROR--Helping children overcome fear of dental treatment is the goal of two new projects recently funded by the National Institute of Dental Research. The first study will be by Barbara G. Melamed, Ph.D., at Case Western Reserve University, Cleveland. Dr. Melamed and three dentists, Drs. Roland Hawes, Steven Hutcherson, and Richard Hirschman, will determine the benefit to children undergoing dental treatment of a combination of an explanatory film and specific behavioral approaches by the dentist.

In the second study, a Connecticut pedodontist, Larry L. Venham, D.D.S., Ph.D., will determine whether children's age and need for treatment on their first visits to the dentist affect anxiety and behavior on subsequent visits. More than 200 children, ages two to five will participate. Half will require treatment at the beginning of the study and half will not, but all will most likely need some treatment during the three-year study.

When the children visit the University of Connecticut's dental clinic in

(more)

Farmington, closed circuit television will film their behavior. To measure anxiety, video tapes, physiological measures, and a self-report will be used. With the report, which is designed for the very young, children select the cartoon character that best matches their own feelings.

- - -

NTA STUDIES--The results of recent scientific studies on the general toxicity and carcinogenicity of nitrilotriacetic acid (NTA) were discussed at an open meeting at NIH on August 13. NTA has been considered as a substitute for phosphates used as building agents in detergents. Its use in the United States was discontinued four years ago. The toxicity results discussed at the meeting came from one study conducted by the National Institute of Environmental Health Sciences, and two studies sponsored by the National Cancer Institute Bioassay Program. Copies of the results of the studies were distributed at the meeting.

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Editors of publications may request a glossy print of the numbered photographs that appear in this issue.

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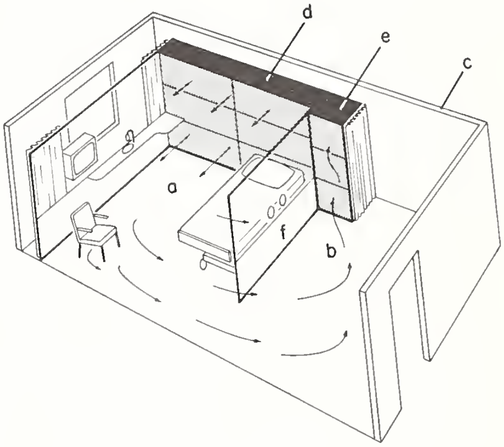
September 10, 1975



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Research Advances

RAPID TYPING TECHNIQUE IDENTIFIES SPECIFIC LD TRANSPLANT ANTIGENS

Graft rejection -- the major problem in transplantation today -- may decline now that National Institute of Allergy and Infectious Diseases grantees at the University of Wisconsin have developed a technique by which donors and recipients can be rapidly typed for specific lymphocyte-defined (LD) antigens.

Identification of these antigens should result in better matched transplants, especially those involving cadaver kidneys, and should also facilitate the worldwide exchange of transplant organs and bone marrow.

Surgeons can successfully transplant a heart, kidney, or other organ but the graft may fail if the body's immune system recognizes it as foreign. To minimize this foreignness, scientists usually select the most compatible donor on the basis of serological techniques which detect the two known systems of major tissue-matching antigens.

One technique, HL-A typing, can specifically identify the serologically-defined (SD) antigens on donor and recipient white blood cells. The mixed leucocyte culture (MLC) test, however, can determine only that different lymphocyte-defined (LD) antigens are present on donor and recipient cells. It cannot specifically identify these antigens. This limitation, as well as a necessary four to five day wait for results -- longer than a cadaver kidney can survive -- has prevented widespread use of MLC for transplant matching.

The Wisconsin scientists have now overcome these problems with development of their new test, primed lymphocyte typing (PLT). Using this test, scientists can identify specific LD antigens in only one or two days.

PLT is based on the MLC test principle that a recipient's purified white

(more)

blood cells multiply when mixed with a donor's purified cells bearing different LD antigens. However, in developing the PLT, the scientists used test cells "primed" to recognize a specific LD antigen. Thus, in the PLT test, when this specific antigen is present on the cells of a prospective organ recipient or donor, it will restimulate the test cells to rapid multiplication.

Using appropriate families whose members differ by only one LD antigen, scientists should be able to compile a panel of appropriately primed blood cells which will recognize all the LD antigens, according to the researchers. Since these PLT cells can be prepared in advance and frozen, the scientists envision the development of typing trays which could be used to rapidly type anyone in the world for LD antigens, as is now possible with SD antigens, thus facilitating choosing the best-matched organ for every recipient.

Another important use for LD typing may be in the diagnosis of human disease, since certain LD antigens have been associated with immune diseases in man, and with cancer viral infections in the mouse. PLT may also prove to be a valuable tool for exploring the function and structure of the major histocompatibility complex, the genetic region that appears to control the antigens important in graft rejection.

The researchers, Michael J. Sheehy, Paul M. Sondel, Marilyn L. Bach, Rudolf Wank, and Fritz H. Bach (the major developer of the (MLC),described their new test in the June 27, 1975 of *Science*.

#

Research Advances

DRR FINDS COMMONLY USED DRUG MAY CAUSE SOME BIRTH DEFECTS

A commonly used drug can possibly cause birth defects when given during the early and middle parts of pregnancy, according to reports made by researchers working with nonhuman primates at the California Primate Research Center, Davis.

The drug, called triamcinolone, is a synthetic corticosteroid which is used for treatment of arthritis, allergies, and skin disorders in humans.

The application of the drug to a group of mature bonnet and rhesus female monkeys and female baboons resulted in still births and severe defects of the skeleton of the offspring (especially the head, face and legs), and of the lymphoid system.

The research group at the NIH Division of Research Resources-supported primate research center has determined that the skeletal defects were caused when the drug was given during the first 50 days of pregnancy. Lymphoid system defects occurred when the drug was given from the 40th to the 133rd day of pregnancy.

"Defects of the skeleton by this drug had been observed in previous laboratory animal experiments, but the defects of the lymphoid system had not been observed previously," chief investigator Dr. Andrew G. Hendrickx reported.

"The lymphoid system, and especially the thymus gland, which was the most severely affected, is important in the immune or disease-fighting system of the fetus and newborn, and plays a major role during the first several years of life," he said. "The development of the lymphoid occurs later in the development of the embryo than other systems and consequently is more susceptible to harmful agents later in pregnancy."

(more)

The drug effect study indicates that the danger of birth defects from triamcinolone may actually be the greatest during the middle months of pregnancy.

In the latest study, the drug was administered to 20 rhesus monkeys, five bonnet monkeys, and six baboons. The scientists also followed the offspring of ten untreated mothers from each species control.

In the monkeys treated with the drug during early pregnancy, gross defects showed among the fetuses just as expected. There were still births, severe malformations such as cleft palates, deformed facial bones, fused fingers and toes, webbed fingers, liver cysts, and malformed kidneys.

When pregnant mothers were injected at periods equivalent to the second trimester (4th, 5th and 6th months of human pregnancy), the birth defects continued to show in the offspring.

In addition, in most of the hormone-treated monkeys, the fetal thymus glands were badly stunted and almost completely unable to produce lymphocytes, the cells critically important to the development of immunity.

The researchers contend that the pharmaceutical manufacturers should emphasize complete abstinence from the drug during the entire pregnancy period.

"The warning regarding use should be expanded through the entire period of pregnancy because of the potentially harmful effects of this drug in the immune system," Dr. Hendrickx said.

The findings in this study on birth defects caused by the use of triamcinolone were published in the July 1975 issue of *Federation Proceedings*.

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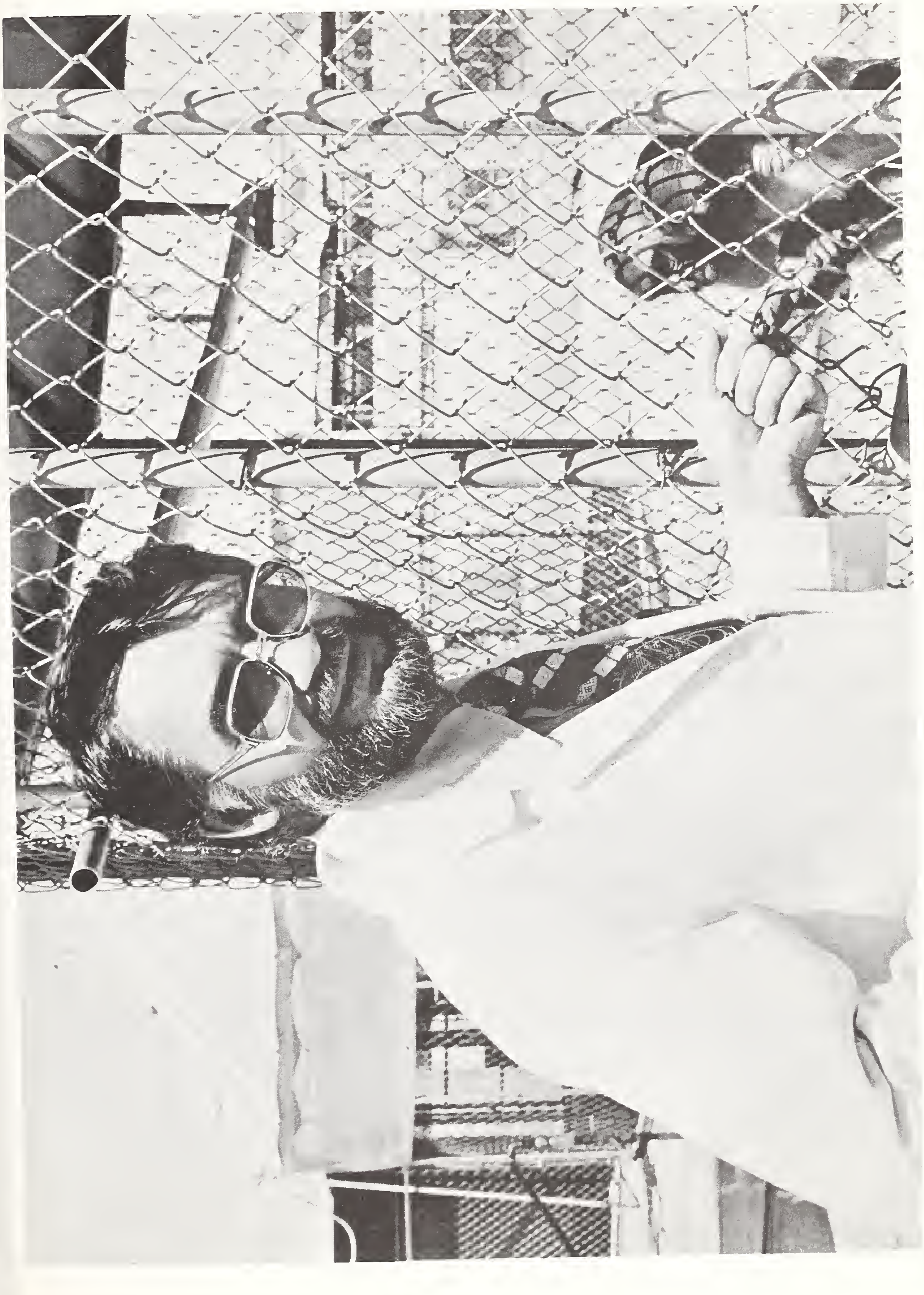
BIRTH DEFECTS (Cont'd)



Dr. Andrew G. Hendrickx is shown with rhesus monkeys similar to those used in testing drugs during pregnancy for birth defects. (NIH Photo # 1446)

#

Research Advances

GALLSTONES DISSOLVED BY COMBINATION TREATMENT

Research shows that a combination of phenobarbital and chenodeoxycholic acid (CDCA) is more effective in dissolving cholesterol gallstones than phenobarbital alone.

In a study conducted at the Cedars-Sinai Medical Center, Los Angeles, CDCA and phenobarbital, either singly or in combination, significantly decreased biliary cholesterol saturation, but gallstone size decreased significantly only in patients treated with CDCA alone or CDCA combined with phenobarbital. Phenobarbital alone was ineffective in gallstone dissolution.

Leslie J. Schoenfield, M.D., a grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases, and his colleagues found that CDCA dissolves cholesterol gallsones by replenishing the bile acid pool and by decreasing hepatic synthesis and secretion of cholesterol. Because phenobarbital has similar actions, they designed a study to compare the relative efficacy and safety of CDCA and phenobarbital on the dissolution of gallstones.

They divided 36 patients with asymptomatic cholesterol gallstones into four groups of eight to 10 patients. They treated each group for one year with either CDCA, phenobarbital, a combination of the two, or a placebo. They compared the effects of the therapies on biliary lipids and on gallstone size.

Treatment with CDCA, phenobarbital, or the combination markedly decreased biliary cholesterol saturation, but this effect was much greater with CDCA and the combination than with phenobarbital. Gallstone size decreased more

(more)

than 50% in nine of 20 patients receiving CDCA, either alone or combined with phenobarbital, but in no patient receiving only phenobarbital or placebo. Gallstones disappeared completely in two patients receiving the combination. Abnormalities in liver-function tests and in liver biopsies occurred with equal frequency in the four treatment groups.

The researchers will continue to compare CDCA therapy with combination therapy in an effort to further investigate the effect of both treatments on gallstone dissolution.

A report of their findings is published in the *New England Journal of Medicine*, June 12, 1975.

#

SALIVA SERVICES--Although taken for granted or ignored by most people, saliva gives us valuable silent services. Perhaps its most vital role is to moisten foods for swallowing. Another function is to begin the digestion of starch. Saliva also helps protect teeth from decay-causing bacterial acids, and washes away unattached bacteria that can cause disease, according to the National Institutes of Health.

#

Research Advances

PREPARATIONS RICH IN ANTIBODIES MAY IMPEDE NATURAL IMMUNITY

Recent studies in the area of hepatitis research indicate that serum gamma globulin preparations rich in antibodies against hepatitis B provide protections against the disease. Investigators report, however, that the protection may be transient and may even impede the development of natural immunity which results from exposure to the hepatitis B antigen.

Alfred Prince, M.D., of the New York Blood Center and George F. Grady, M.D., of Tufts University conducted separate clinical trials in which they tested three preparations to determine an effective protection against the disease. Their work was supported by the National Heart and Lung Institute.

Dr. Grady worked with 712 medical and laboratory personnel who had been accidentally exposed to hepatitis B infections; Dr. Prince studied 614 recently admitted patients or recently hired employees at renal dialysis units, locations of greater-than-normal risk to exposure.

The researchers used as a control normal human gamma globulin which contains the antibodies produced after exposure to antigens, and contains a low level of antibodies against the hepatitis B virus. The other two preparations came from donors who had been exposed to hepatitis B and whose gamma globulin fractions contained either intermediate or high levels of antibodies against the disease, depending on their level of immunity when the blood was withdrawn.

Hospital personnel accidentally exposed to hepatitis B each received 3 ml. of one of the three gamma globulins within a week after exposure and the same injection again after one month. The incidence of hepatitis was seven percent

(more)

among those receiving normal gamma globulins. Those who were injected with the intermediate preparation had a similar occurrence. But the subjects who received preparations high in hepatitis B antibodies experienced only a two percent incidence.

The patients and employees of the dialysis centers received an initial dose of 3 ml. of one of the three preparations, then a similar dose after four months. A pattern similar to the hospital personnel group resulted. Among those patients who received the normal gamma globulin preparation, the incidence of hepatitis was 21.3 and 23.1 percent respectively, but among those who received the preparation high in antibodies it was 7.9 percent.

The trend was the same among the staff. A number of late cases of hepatitis was seen in the accidentally exposed recipients. These late cases raise the possibility that passive immunization may merely defer hepatitis onset or interfere with production of "native" antibodies.

The results indicate that gamma globulin fractions high in antibodies offer significant degrees of temporary protection against the disease, but they may interfere with the acquisition of natural immunity in some subjects.

The investigators reported their findings at the July, 1975 meeting of the International Society of Blood Transfusion.

#

Research Advances

SALINE LAVAGE METHOD APPEARS EFFECTIVE

In a recent study, scientists evaluated the efficacy and patient acceptability of the saline lavage method of cleansing the bowel prior to X-ray examination. They found that saline lavage is rapid, effective, and more comfortable than the standard procedure of castor oil and enemas, and is preferred by most patients.

The standard cleansing procedure in preparing the colon for diagnostic studies includes dietary restriction, purgatives, and cleansing enemas. These are time consuming, often uncomfortable for the patient, and frequently unsuccessful. Castor oil preparations together with enemas have been reported to produce good results in only 32 to 62 percent of cases.

Arnold G. Levy, M.D., of the National Institute of Arthritis, Metabolism, and Digestive Diseases, and colleagues at the NIH Clinical Center made a study to evaluate the effectiveness and acceptability of the saline lavage method. They randomly assigned 75 patients requiring barium enemas to a control group and an experimental group. They imposed two days of dietary restrictions upon the control group prior to oral administration of castor oil and administration of cleansing enemas. No dietary restrictions were imposed upon the experimental group.

Lavage patients ingested four liters of an isosmolar, room temperature salt solution. Total preparation took approximately three hours which was 60 percent less than that for the control group. The procedure proved to be successful for 85 percent of the patients capable of completing the preparation

(more)

SALINE LAVAGE (Cont'd)

and preferred by 76 percent of the patients who had previously experienced a castor oil cleansing preparation.

Because 11 percent of the patients could not consume an adequate (4 liter) lavage volume, the overall success rate of lavage cleansing was less than with the castor oil method (76 percent vs. 95 percent).

Lavage patients, however, experienced less overall discomfort, especially in regard to dietary restrictions, loss of sleep, and administration of enemas. Three to one preferred lavage over castor oil. No significant changes were noted in serum electrolytes with either procedure, despite dehydration produced by castor oil and hydration produced by lavage.

The two major disadvantages to the lavage method are the inability of some patients to consume an "adequate" volume and the limitation to patients without cardiovascular or sodium balance problems.

The investigators' studies suggest that the lavage method may be useful in cleansing the colon of patients with inflammatory bowel disease in whom purgatives are contraindicated. Additional preliminary studies revealed that lavage may also be useful in cleansing the colon for colonoscopy, thereby eliminating two to three days of dietary restrictions.

The researchers report their findings in a coming issue of *Gastroenterology*.

#

Photo Feature

NIH LAMINAR AIR FLOW ROOMS HELP PROTECT SOME PATIENTS

Infection is a major cause of death in patients with diseases such as leukemia. It often threatens these and other patients who may be unusually infection-prone because of their diseases or treatment.

To decrease this threat, investigators at the National Institutes of Health are testing laminar air flow rooms in which infection-prone patients may live temporarily in a clean-air environment.

The atmosphere in laminar air flow rooms in NIH's research hospital, called the Clinical Center, is kept 99.97 percent sterile by a specially-designed air filter system. Normal hospital air is drawn through two sets of filters before arriving in the patient module. From the filters at the head of the patient's bed, air flows horizontally across the room and out the door, carrying with it air-borne micro-organisms.

To limit entry of people into the flow rooms, medical examinations are performed from outside with the use of gloves installed in a curtain-wall, made of transparent pliable polyvinyl,located adjacent to the bed. Acoustic design permits staff and visitors to talk with the patient through the vinyl curtain.

When it is necessary for hospital staff members to enter the room, they don protective, disposable gowns, gloves, boots, masks, and caps, and they remain "downwind" of the patient. All items used for or by the patient are sterilized -- even personal items like books and guitars.

A bedside monitor records blood pressure, pulse, respiration, and heart

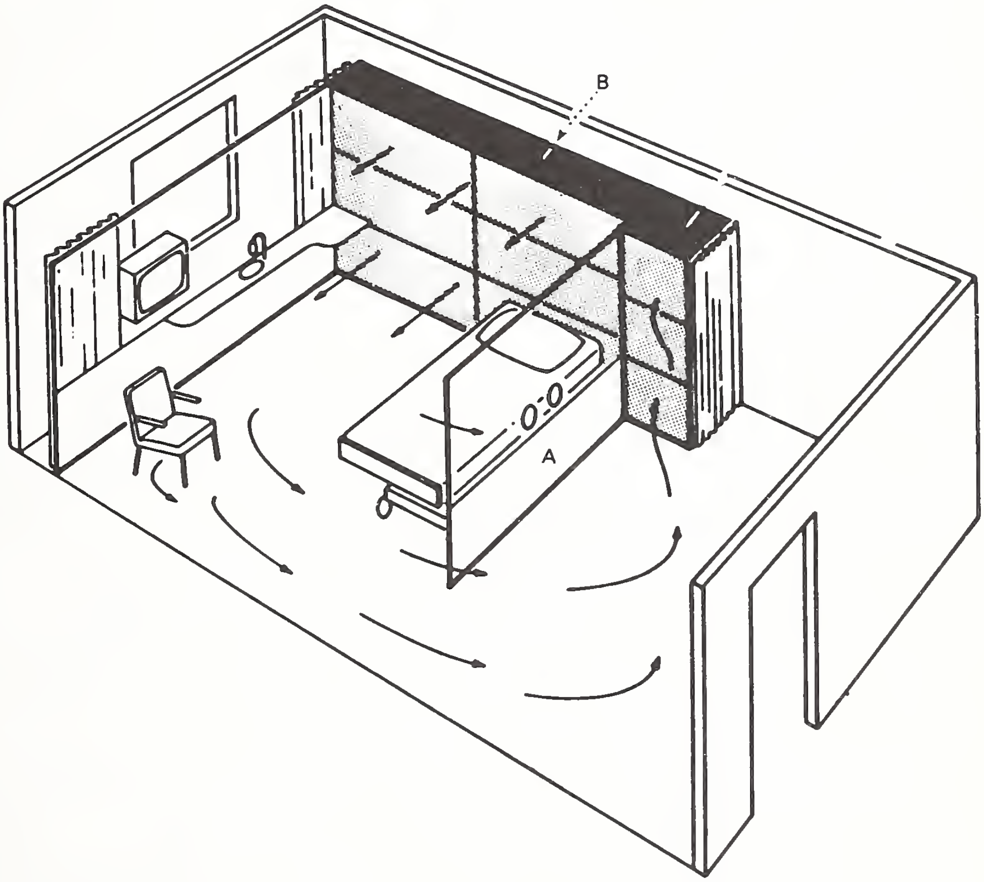
(more)

LAMINAR AIR FLOW (Cont'd)

rate, and the patient can be observed from the nursing station via closed-circuit television.

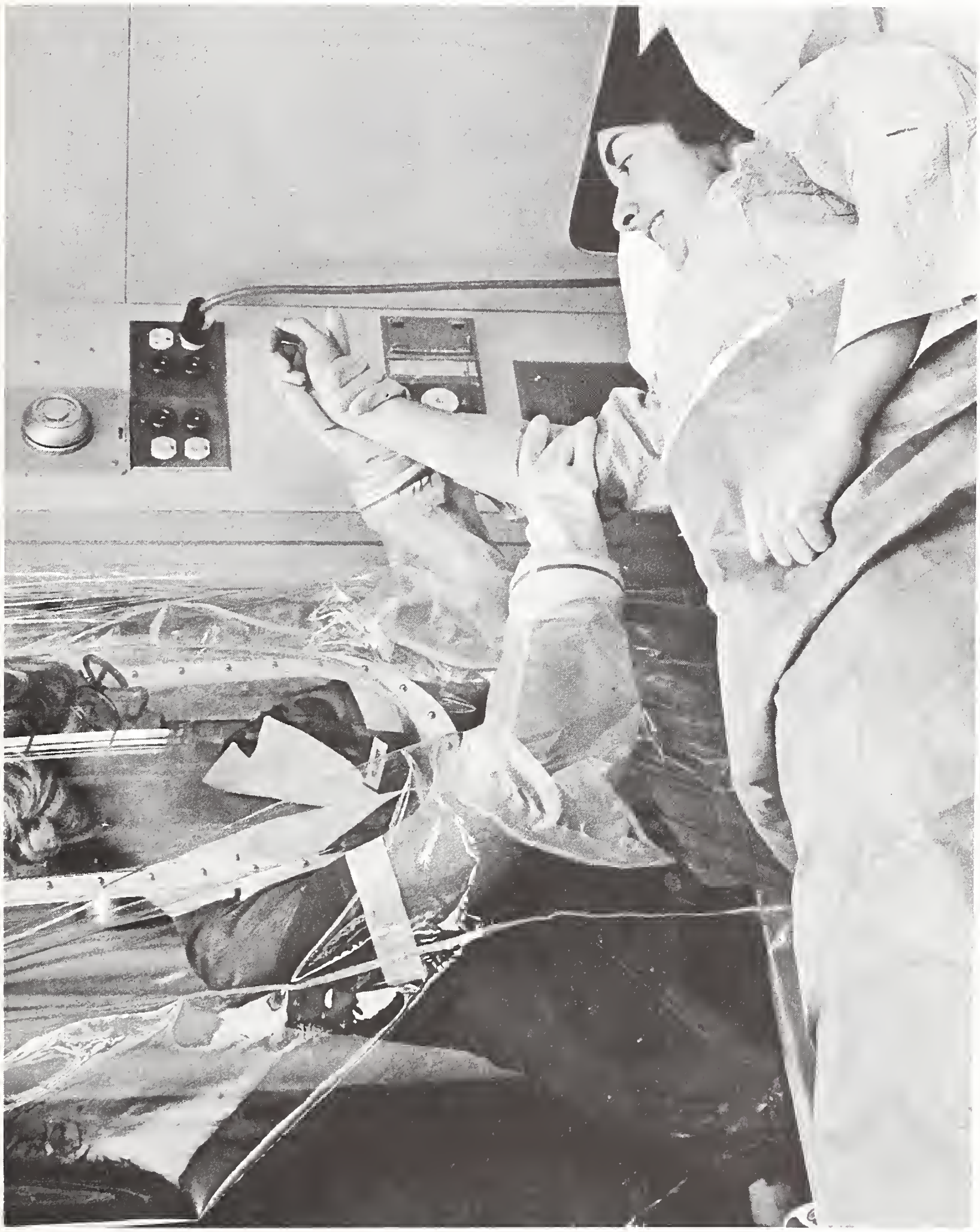
Meals are specially prepared on the nursing unit by members of the Clinical Center Nutrition Department and served on sterile dishes and trays.

The patient is free to move around the room, and can control privacy drapes, turn on the closed-circuit television set, and talk with other patients on the unit or the nurses on duty at the nursing station.



The room is specially designed to provide the infection-prone patient with a temporary 99.97 percent sterile atmosphere in which to live. The front wall of the room (a) is made of a transparent polyvinyl curtain with flexible glove ports. The glove ports may be used by hospital staff and visitors for easy access to the patient. Large air filters (b) are located at the head of the patient's bed to draw normal air into the filters and circulate sterile air throughout the room. (NIH Photo # 1447)

LAMINAR AIR FLOW (Cont'd)



The glove ports in the plastic vinyl curtain provide easy access to patients by hospital staff members such as the inhalation and physical therapists. Exercise therapy is possible because the glove ports provide a flexible range in which to work with the patient. The ports and curtain also enable the patient to maintain close contact with family members during the hospital stay. (NIH Photo # 1448)

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Hospital staff members wear protective, disposable gowns, gloves, boots, masks, and caps before entering the flow room. (NIH Photo # 1449)

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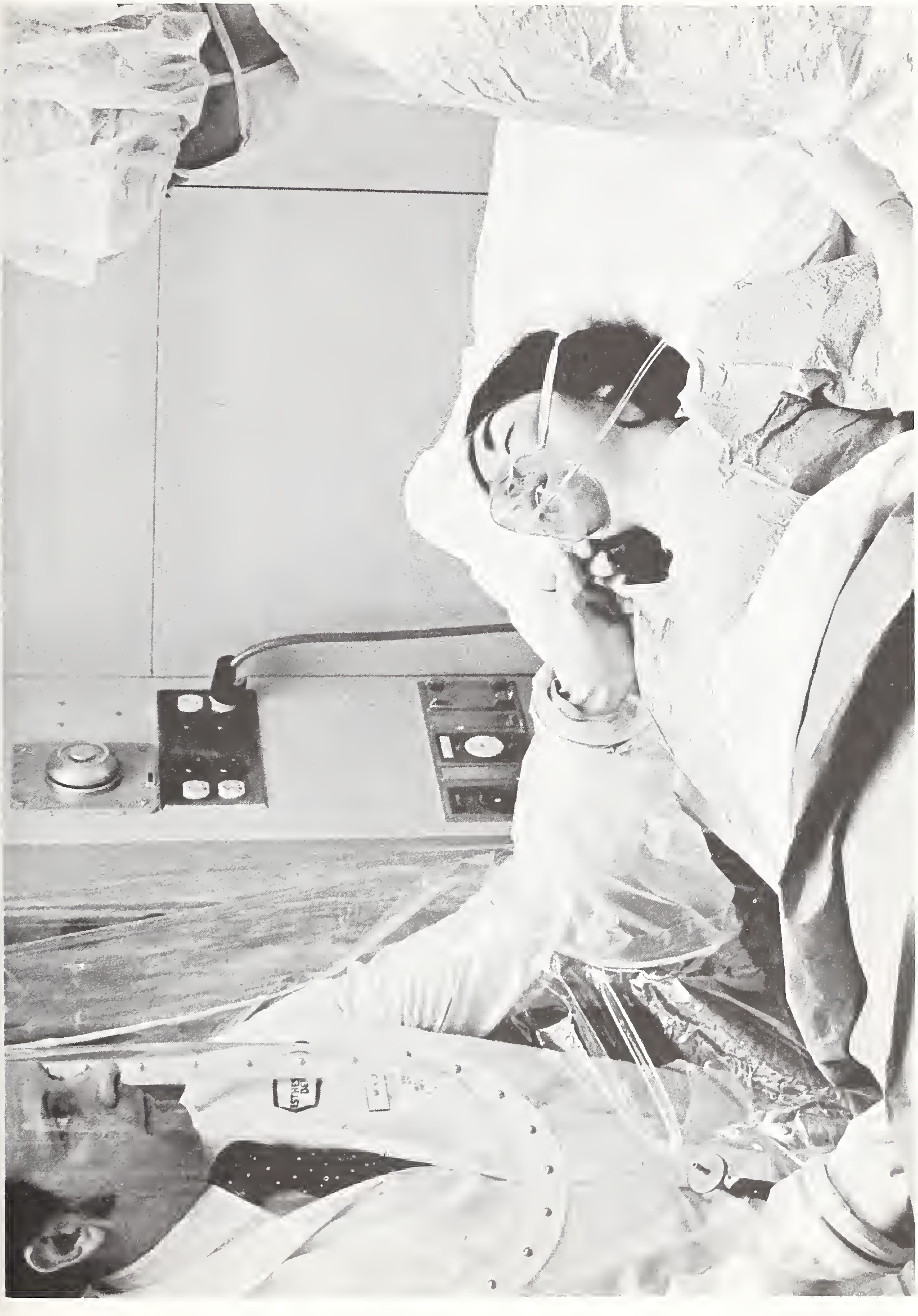
LAMINAR AIR FLOW (Cont'd)



Medical personnel have access to the patient through the glove ports (left) or by entering the laminar air flow room. (NIH Photo #1450)

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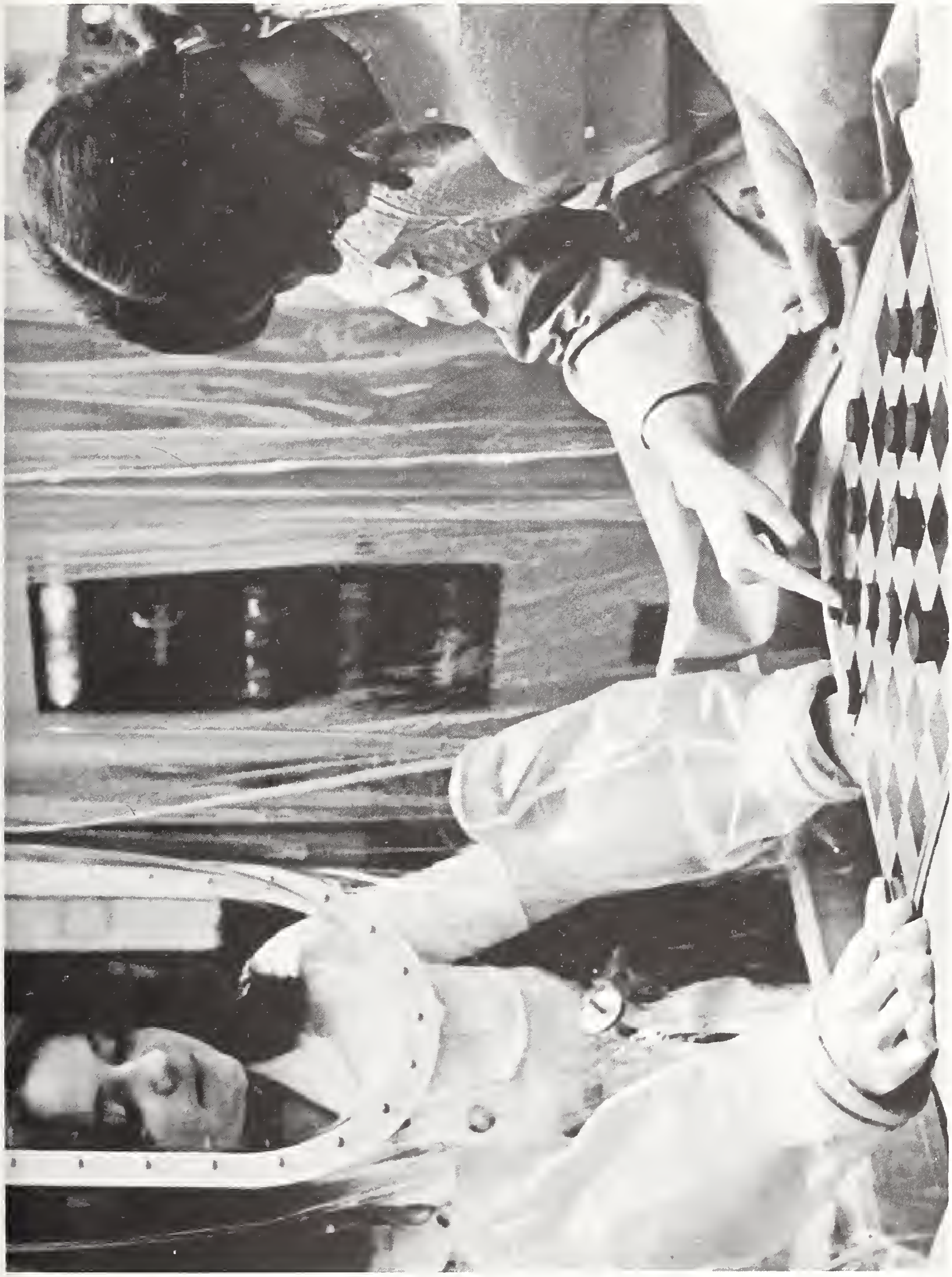
LAMINAR AIR FLOW (Cont'd)



Using glove ports, a recreational therapist (left) plays a game of checkers with a patient. Art and crafts projects and games are offered to the patient for entertainment and, more important, to provide interpersonal contact for patients confined to these rooms. (NIH Photo # 1451)

#

Photo Feature

MARKMAN TUTORENDOSCOPE IS ON DISPLAY AT NLM

The Markman Tutorendoscope, developed by Dr. H. David Markman of the department of surgery, Albert Einstein College of Medicine, is currently on display in the National Library of Medicine.

The instrument gives medical students and physicians--in the absence of patients--a simultaneous viewing of slides through a simulated proctosigmoidoscope on an 18 inch screen, enabling them to study the appearance of both normal and pathologic conditions of the anus, rectum, and colon.

Each slide is numbered to correspond with an index card giving information on the patient's age, sex, symptoms, and depth of penetration at the time the lesion was photographed. These may be detached from the unit for testing.

The tubular environment of the sigmoidoscope permits economical, concentrated learning in minimal time, under conditions closely simulating clinical practice. The tutorendoscope is very advantageous in that it can be used at any time without interfering with schedules of patients, physician-instructors, students. Also it eliminates any embarrassment or discomfort to the patient. In addition, the device can be used to train students to perform passage of the proctosigmoidoscope and the fiberoptic colonoscope without harm or discomfort to the patient.

The development of the tutorendoscope was supported by the National Cancer Institute, the American Association for Cancer Education, and the New York City Division of the American Cancer Society.

Cancer of the colon and rectum is the most frequently occurring internal cancer common to both sexes. More than 79,000 Americans developed colon and rectum cancer in 1973; approximately 47,000 died of their disease. Three out of four of the patients might have been saved by early diagnosis, including

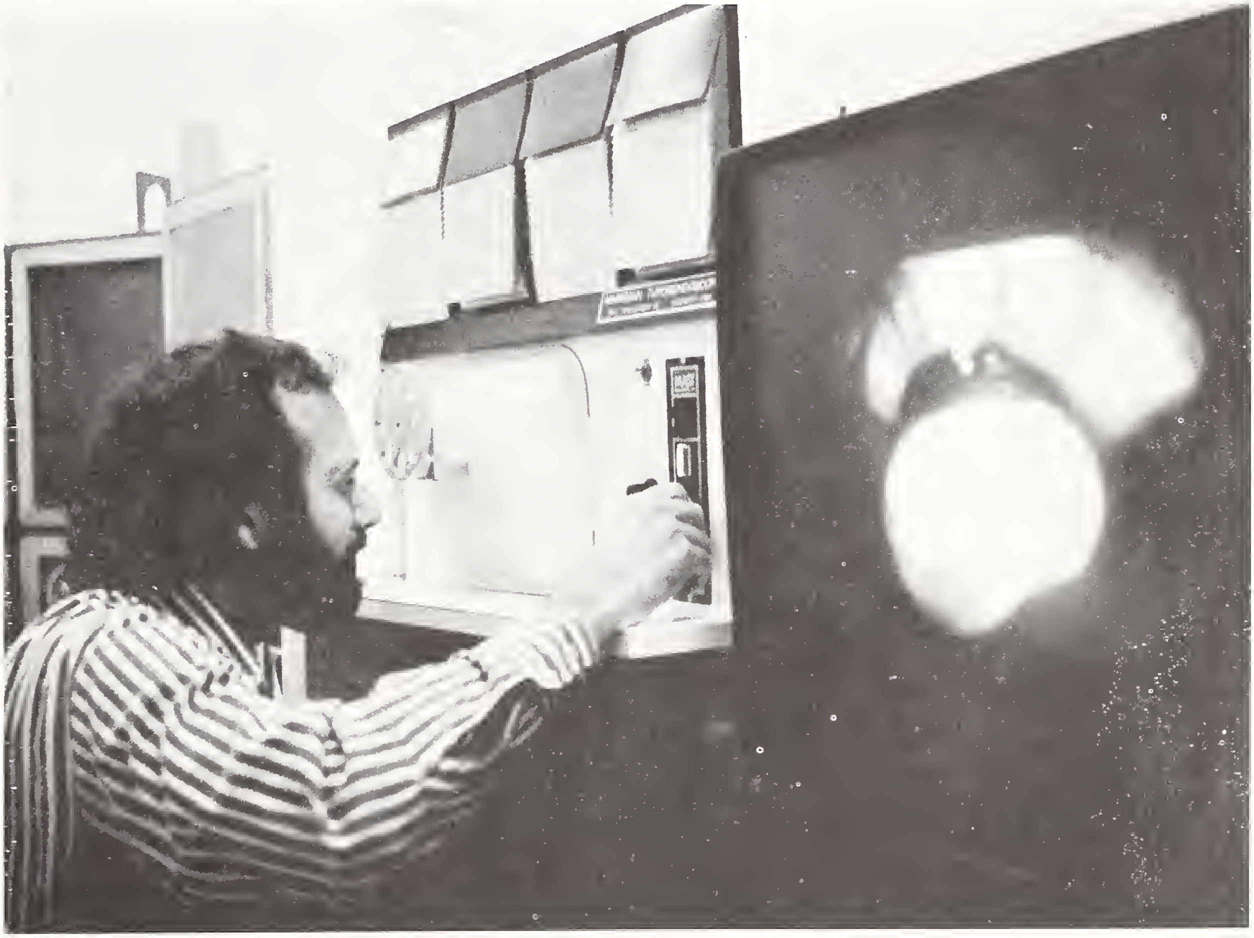
(more)

TUTORENDOSCOPE (Cont'd)

a proctosigmoidoscopic examination, and prompt treatment.

Medical educators have been aware of the necessity for teaching proctoscopy; however, the difficulties of instructing each student individually include problems of time, effort, scheduling, patient participation, and availability of a variety of lesions.

Currently, most doctors do not examine the lower bowel unless the patient has symptoms of bleeding or change in bowel habits.



The Tutorendoscope permits simultaneous viewing of slides through a simulated proctosigmoidoscope and on an 18-inch square screen. Numbers on the slides, showing normal and pathologic conditions, correspond with index cards giving full clinical details, which may be detached from the unit for testing. (NIH Photo # 1452)

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NEWS & FEATURES From NIH September 10, 1975

Photo Feature

ONE DENTAL CEMENT MAY EXCEED THREE OTHERS

Zinc silicophosphate cement proved more unaffected by wear and dissolved less rapidly in patients' mouths than three other cements tested during a one-year clinical study made at the University of Oregon under a National Institute of Dental Research grant.

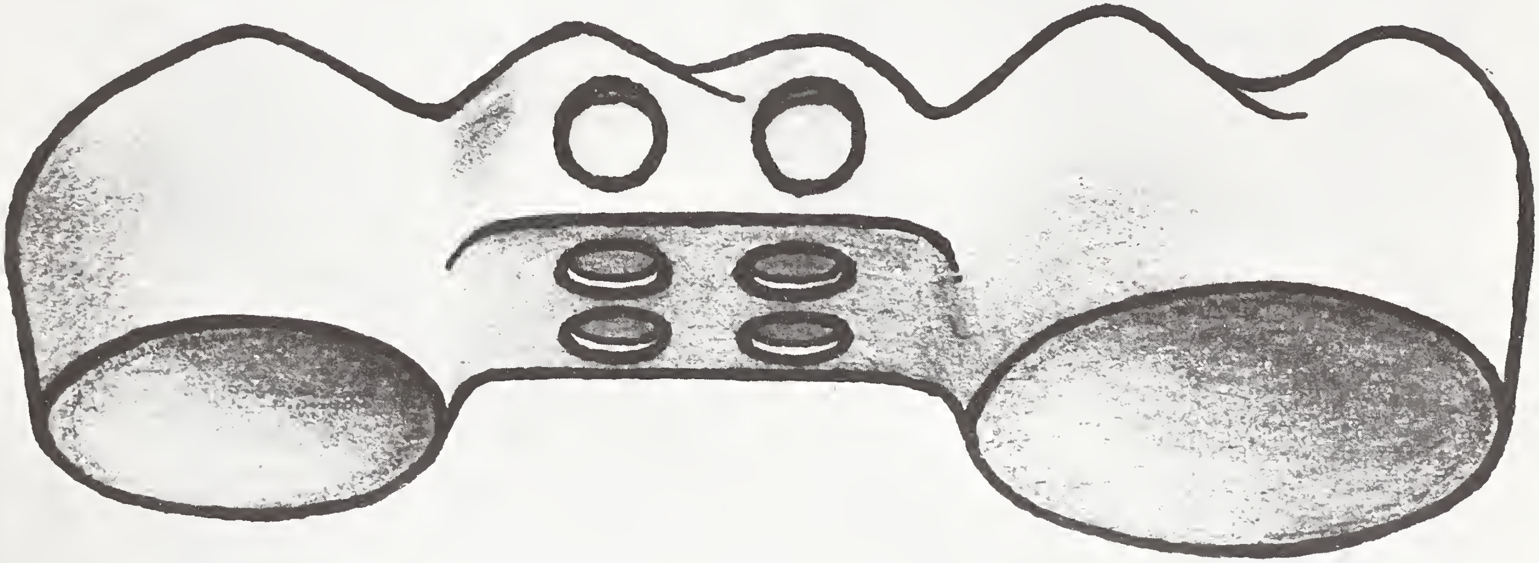
The dental cements were tested in standard cavities made in fixed partial dentures. Four identical holes were drilled into the side surfaces of each bridge facing either the tongue or cheek where abrasion from brushing, chewing and other motions occur, and four others were located under the bridge where the cements were exposed only to mouth fluids.

The scientists found that zinc silicophosphate was the most durable cement, with zinc phosphate ranking second. The other two, zinc polycarboxylate and zinc oxide and eugenol with alumina, dissolved equally fast and more rapidly than the first two cements. All cements placed under bridges where no wear occurred also dissolved in mouth fluids, but were found to degrade faster with wear.

The investigators, William A. Richter, D.M.D., now at UCLA, and Hiroshi Ueno, D.D.S., evaluated each cement's durability by comparing photographs of obliquely-lighted, silver-plated models of impressions of the dentures made before and one year after placement in patients' mouths.

These findings differ markedly from previous laboratory tests with distilled water. In water, zinc silicophosphate was most soluble and zinc polycarboxylate was least affected. The scientists were not surprised to find that cement dissolution varied considerably in different patients because saliva and other substances in the mouth differ widely.

This research was reported in the *Journal of Prosthetic Dentistry*, March, 1975.



This is a schematic sketch of the design of fixed partial dentures used for evaluation of cements. Shown are the cavities or receptacles into which the cement specimens were placed. (NIH Photo # 1453)

#

Research Illustrated

MEDICAL "SCREENING," "ANXIOUS" PATIENTS, AND THOUGHT FOR FOOD

Some medical subjects lend themselves to teaching via audiovisuals. The Multimedia Resource Center in the National Library of Medicine's Reading Room has a collection of 1,200 motion pictures, videotapes, cassette audio tapes, and self-teaching audiovisual kits for medical education purposes. (NIH Photo #1454)

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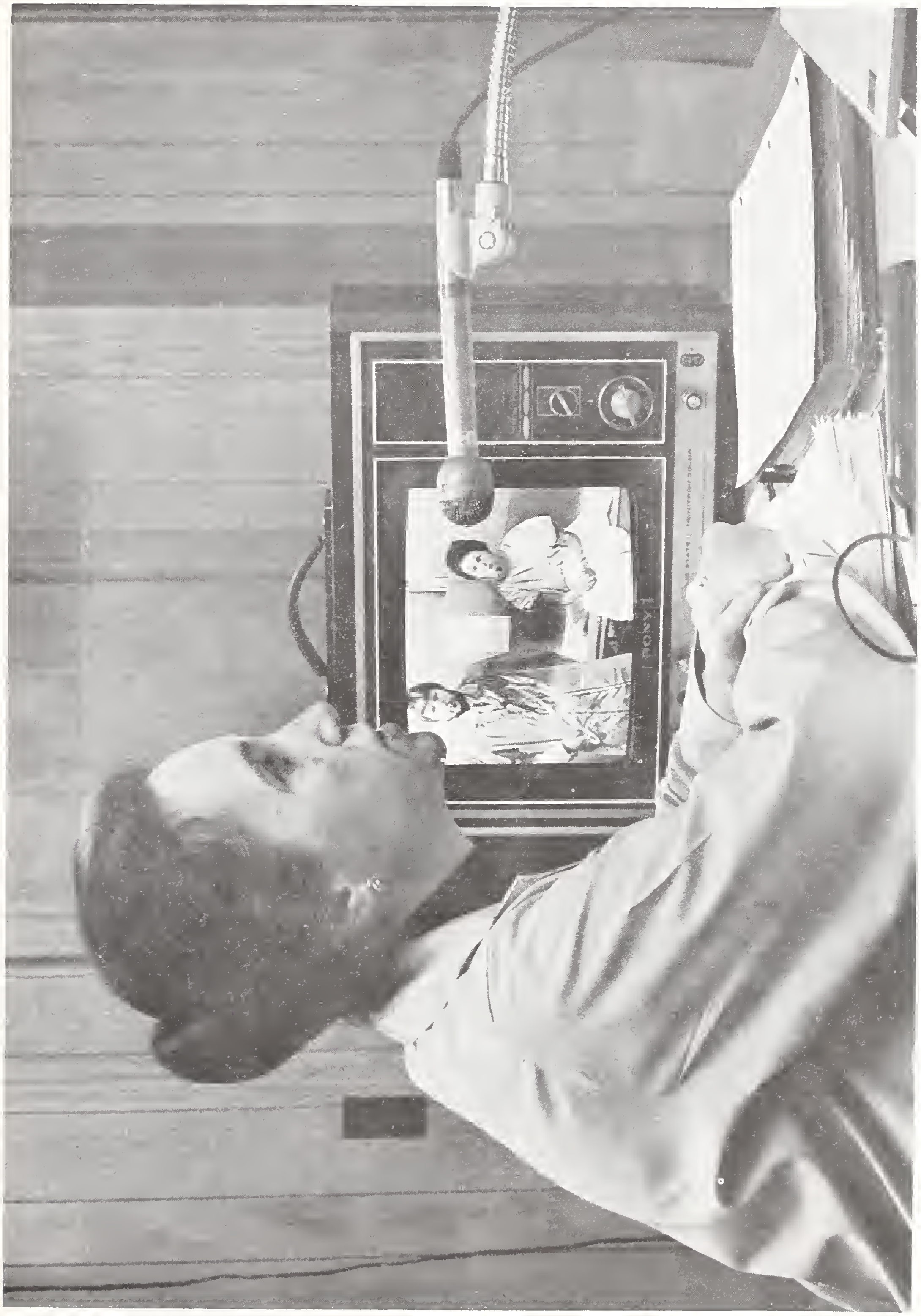
RESEARCH ILLUSTRATED (Cont'd)



Another audiovisual technique is the use of closed circuit television to bring patients in touch with physicians at a medical center that is many miles from the patients. A dermatologist at the University of Vermont is "examining" a patient in a small community that is 65 miles away. (NIH Photo #1455)

(more)

This young lady and the other one on the following page are not too sure what to expect from modern medical research advances. But they and their generation are benefiting from the practical application of latest research findings to the practice of medicine. (NIH Photos #1456 and #1457)

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(See caption on previous page.)

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RESEARCH ILLUSTRATED (Cont'd)

The National Institute of Environmental Health Sciences studies marine species that are sensitive to pollutants so that the scientists can learn about potential human hazards. These clams will be subjected to careful testing. (NIH Photo #1458)

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RESEARCH ILLUSTRATED (Cont'd)

Rats that reside in special environmentally-controlled chambers are fed a sugar-rich diet and infected with **S. mutans**, *derived from human carious lesions. The rats become victims of tooth decay. The National Institute of Dental Research has studied the results of such research.* (*NIH Photo #1459*)

#

Disease Profile

DIETARY CONTROL WILL USUALLY HELP HYPOGLYCEMIA PATIENTS

Hypoglycemia is a technical term meaning a level of sugar (glucose) in the blood which is lower than normal. It usually occurs several hours after eating, and is manifested variously by sweating, trembling, palpitation, hunger, weakness, and lightheadedness. These symptoms may vary in duration and often disappear rapidly after eating a snack, a sweet, or drinking a glass of milk, according to the National Institute of Arthritis, Metabolism, and Digestive Diseases.

If the condition is not relieved, a further lowering of the blood sugar level may occur, leading to headache, irritability, and loss of mental acuteness. Some patients with neuroses and other psychiatric disorders have symptoms simulating those of hypoglycemia. Continuing fatigue and anxiety, however, are seldom, if ever, due to hypoglycemia. A few rare, severe, uncontrolled cases of "low blood sugar" may progress to visual and speech disturbances, convulsions, coma, and death.

Blood sugar levels are regulated by the interplay of many factors, chief among which are the intake of carbohydrates in the diet--all of which are converted to sugar by digestion--and the action of the hormone insulin produced by the pancreas, a gland lying behind the stomach. Insulin acts to facilitate the entry of sugar (glucose) into the cells of the body, thus providing much of the energy required for normal body functions. The brain, in particular, requires a constant supply of sugar from the blood for its normal activity.

Most cases of hypoglycemia result from overproduction of insulin by the pancreas, and are manifested by symptoms similar to those which occur when a diabetic patient takes too much insulin or an excess of antidiabetic pills.

(more)

There are, however, many other causes. Alcoholic excesses can cause hypoglycemia that does not seem to involve insulin excess.

In about 70 percent of cases of hypoglycemia the cause is of a functional nature: blood sugar is burned up too rapidly, but no organ or tissue of the body is anatomically abnormal. These cases are usually not too serious, rarely progress, and often become less severe with passing years. Rarely, hypoglycemia is an early manifestation of diabetes mellitus.

Functional hypoglycemia responds best to a diet high in proteins and low in carbohydrates, which usually is divided into six equal meals throughout the day. Individuals subject to such attacks should always carry some sweets with them for use in emergency situations.

Hypoglycemia may also result from a number of organic causes, such as a tumor of the pancreas, a damaged liver, and other glandular or metabolic disturbances. Definitive treatment of such cases depends on the specific cause of the low blood sugar level, and may be either medical or surgical. Loss of time in recognizing and treating these cases may allow a disease to progress too far to be curable.

The diagnosis of hypoglycemia is complicated by the fact that the typical symptoms of the disorder are also characteristic of a large number of other conditions. It is usually diagnosed by demonstrating low blood sugar levels during an attack, and by the dramatic relief which usually follows the administration of sugar.

If such blood tests demonstrate that the condition is present, it is imperative to identify the underlying cause responsible for the low blood

(more)

sugar levels. A thorough medical examination is required in order to identify and correct any organic factors which may be contributing to the condition.

Although diet alone will often keep low blood sugar levels under control, treatment of this disorder should never be on a do-it-yourself basis. Only the physician who has examined a hypoglycemic patient and who is familiar with his medical history and with pertinent laboratory data is in a position to determine what factors are causing his condition and to prescribe treatment.

In recent years a number of unfounded claims have been made for a single "cure" for hypoglycemia of all causes. The so-called "cure" usually takes the form of a special diet, which closely resembles the high protein-low carbohydrate diet used in treating functional hypoglycemia. Such self-prescribed, blanket "cures" should be avoided. Moreover, in the quest for followers, some fund-raising organizations have encouraged the belief that hypoglycemia is a cause of diseases ranging from arthritis to schizophrenia, and that treatment necessitates use of potent glandular extracts. Actually, simple dietary control is usually sufficient.

#

HUMAN BODY--The mature human body is the end result of nearly 20 years of growth. Each individual begins as the product of two cells and eventually is made up of 100,000 billion cells, according to the National Institutes of Health. The most rapid and crucial period of growth in the human being occurs in the nine months before birth.

#

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Research Advances

HUMAN ALLERGIC RESPONSE TO RAGWEED REQUIRES BOTH T AND B CELLS

Laboratory experiments carried out by some National Institutes of Health grantees in Boston have established the helper role of T (thymus-derived) cells in the human allergic antibody response, Furthermore, the investigators suggest that the experimental methods used in their study may be useful in allergy testing and evaluation of treatment.

Although a few allergies, such as reactions to poison ivy, are known to be mediated by T cells, antibodies synthesized by B (bone-marrow-derived) cells play the major role in respiratory allergies, such as hay fever. Animal experiments have shown that, in several species, T and B cell interaction is a prerequisite for the production of the sensitizing antibodies known as IgE. The role of this interaction in human IgE antibody response, however, has not up to now been clear since studies have made use of unfractionated suspensions of lymphocytes.

In the present investigations, T and B cells were separated out of the sera of three ragweed sensitive individuals and three non-sensitive persons. The isolated T cells were then incubated for six days with the principal antigen of ragweed -- known as antigen E. The terminology for ragweed purified fractions (e.g. antigen E) bears no relationship to that for immunoglobulins (e.g. IgE). Only T cells from antigen E-sensitive donors proliferated (synthesized DNA) in response to the ragweed antigen. B lymphocytes from either antigen E sensitive or negative donors failed to proliferate or synthesize antibody in response to the antigen.

However, when B lymphocytes from antigen-sensitive donors were incubated

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with culture fluid from the stimulated T cells, both IgE and IgG antibodies, specific for ragweed antigen, were secreted. The specificity of the antibodies was determined *in vitro* and *in vivo*.

Thus, the present study clearly demonstrates that cooperation between human T and B lymphocytes is necessary for the *in vitro* antibody response to ragweed antigen E, since only those culture fluid supernates from antigen-stimulated T lymphocytes contained an activity that caused B lymphocytes from antigen sensitive donors to synthesize and secrete antibody.

Because the reaction was so specific, the investigators believe the methods used in the investigations could be applied as an *in vitro* test of the antibody response of any individual suspected of allergy to a specific antigen. The test could also be used to determine whether or not treatment was succeeding in decreasing or neutralizing production of troublesome IgE.

Raif S. Beha, Harvey R. Colten, Eveline Schneeberger, and Ezio Merler, Children's Hospital Medical Center and Harvard Medical School, Boston, reported their work in the August 1975 issue of the *Journal of Clinical Investigation*. Their investigations were supported by the National Institute of Allergy and Infectious Diseases, the National Institute of Arthritis, Metabolism, and Digestive Diseases, the National Institute of Child Health and Human Development, and the Division of Research Resources, as well as by the Lebanese National Council for Scientific Research.

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Research Advances

LONG-TERM HEAVY MARIJUANA USE CAN CAUSE "IRRITABLE AGGRESSIVENESS"

A two-year study on the use of marijuana by nonhuman primates at the California Primate Research Center, Davis, indicates that long-term heavy use causes "irritable aggressiveness."

The studies at the NIH Division of Research Resources-supported center revealed a three-stage progression of drug effects on the macaque monkeys treated with the drug, tetrahydrocannabinol (the major component of marijuana), using a dose equivalent to the smoking of 20 marijuana cigarettes by a human every day. The drug was fed to the animals in iced raisin cookies and prunes.

Chief investigator Ethelda N. Sassenrath, Ph.D., reported that the initial stage of drug intoxication persisted for one or two months.

"After the first month, they showed intoxication--a monkey's high," Dr. Sassenrath said. "They were alternately sleepy and restless. Their interest in grooming and play dropped off, and finally there was a marked reduction in interaction with other monkeys."

After two months of marijuana use, the monkeys developed a tolerance to it, and observers could not tell drugged animals from those who were not.

Finally, after six to eight months, characteristics of irritable aggressiveness were noticeable. The monkeys became aggressive, biting and hitting other animals in the same cage. They would only show respect for the group leader, the alpha male.

Dr. Sassenrath confirmed previous findings that no serious physiological defects were detected in the users as a consequence of heavy marijuana dosage.

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"Over the same two-year period of daily drugging, no drug-related changes were observed in stress hormone levels, in sex hormone levels (testosterone in males, and progesterone in cycling females), or in selected measures of cellular immunological responsiveness," she reported.

However, the behavior of the monkeys after several months of daily marijuana use is altered in such a way that they do not have the personality they had before marijuana drug administration. "Humans may or may not react in the same manner," the behavioral biologist said.

With regard to effects on the offspring of heavy marijuana users, Dr. Sassenrath reports that the developing nervous system may be a sensitive target for low levels of the drug. There have been some observations on several offspring which suggests some effect on the brain and resulting behavioral hyperactivity. "These observed effects are of such a nature as to be difficult to substantiate as drug effects in human subjects," Dr. Sassenrath said. "Continued observations in primate test systems can provide relevant information in this relatively unexplored area."

The findings in this study on marijuana use were published in the July 1975 issue of *Federation Proceedings*.

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DIABETES--A complicated disease for which there is no known cure, diabetes ranks seventh on the list of diseases causing death in the United States, according to the National Institutes of Health.

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Research Advances

ASPIRATION TECHNIQUE CAN ANALYZE FETAL CELLS FOR COOLEY'S ANEMIA

A recent study indicates that scientists can use the transabdominal placental aspiration technique, which samples fetal cells, in utero, to analyze the cells for Cooley's anemia (homozygous beta$^+$- thalassemia) and to establish a correct diagnosis of a normal fetus. Investigators reported only last year that fetal blood could be obtained with this method aided by ultrasonography from women who were pregnant for 18 to 22 weeks.

Yuet Wai Kan, M.D., at the University of California, San Francisco, and associates analyzed blood at 20 weeks gestation from a fetus known to be at risk for Cooley's anemia and predicted successfully that the child would be unaffected. Their work was supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases.

A couple of Sicilian origin with heterozygous beta-thalassmeia whose first child had homozygous beta$^+$- thalassemia requiring monthly blood transfusions, requested prenatal diagnosis during a second pregnancy. The placenta was localized posteriorly by ultrasoud at the 20th week of gestation, and was aspirated with a 20 gauge needle. The scientists obtained samples containing fetal red blood cells and performed studies of globin-chain synthesis.

Measurement of incorporation of radioactive leucine into beta and gamma globulin chains revealed a beta/gamma synthesis ratio of 0.083, in the normal range for a gestational age of 20 weeks. Thus, the investigators were able to inform the prospective parents that their fetus was normal or, at worst, a carrier of the thalassemia trait, and that a planned abortion

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would not be necessary.

The infant, born at term, was not affected with homozygous or heterozygous beta-thalassemia. Physical examination of the male infant was within normal limits, and there was no imbalance in globin-chain synthesis (0.96 ratio) as determined by studies of the infant's umbilical cord blood.

The study shows that prenatal diagnosis is rapidly becoming a reality for families at risk for offspring with Cooley's anemia or sickle cell anemia, two of the major inherited hemoglobin abnormalities. The investigators indicate however that more experience in fetal blood acquisition and in the establishment of the safety of this procedure is needed.

They reported their findings in the *New England Journal of Medicine*, July 31, 1975.

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ALLERGY PROBLEM--The symptoms of all allergies are caused by the body's abnormal response to foreign substances called allergens. Each time a person is exposed to the allergen, the irritating allergy symptoms appear, according to the National Institutes of Health. If a person is troubled by bothersome symptoms and suspects he may have developed an allergy, he should consult his family doctor or an allergist, a physician specializing in allergies.

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Research Advances

CHANGES IN RATS' INTESTINES SEEN AFTER INTRAVENOUS FEEDINGS

In a recent study conducted at the University of Texas, scientists working with animal models found that intravenous feeding is associated with decreases in gastrin levels, disaccharidase enzyme activity, and the weights of the oxyntic gland area of the stomach, pancreas and small intestine. They reported, however, that the changes can be largely prevented if gastrin, the deficient hormone, is supplied exogenously.

Leonard R. Johnson, Ph.D., a grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases, and his colleagues described deleterious changes in the gastrointestinal tract of rats fed intravenously. They indicate these changes might eventually be seen in human patients who are fed parenterally.

The scientists fed rats intravenously for three weeks. During that time, their body weight increased by 22 percent, but the weights of the oxyntic gland area of the stomach, small intestine and pancreas decreased significantly. Antral gastrin levels also decreased to one-thirtieth of control levels, and specific and total activities of the different disaccharidase enzymes were only a fraction of normal. No similar changes occurred in rats fed an isocaloric oral diet.

The investigators compared rats fed orally with rats fed intravenously with either a liquid diet alone, or a liquid diet plus pentagastrin, or plus histamine. They found that only pentagastrin prevented the previously observed decreases in weights of gastrointestinal tissues and in the activities of

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disaccharidase enzymes.

They concluded that oral ingestion of food apparently is necessary to maintain the structural integrity of certain tissues of the gastrointestinal tract. They also concluded that the maintenance of normal tissue stores of gastrin must depend on stimuli provided by oral ingestion of food and its presence in the gastrointestinal tract. In addition, it was concluded that the trophic effect of gastrin is apparently necessary to maintain the structural and functional integrity of the gastrointestinal tract.

The scientists published their research in *Gastroenterology, Vol. 68,* May 1975.

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HEAD INJURY--The National Institutes of Health is funding several research projects about head injuries, including an investigation of cerebral blood flow during coma and a separate study of recovery after the acute care phase is passed. The knowledge that irreversible brain damage in survivors is usually a result of the aftereffects of the injury rather than the injury itself makes a special effort in this research immensely worthwhile.

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Research Advances

LABORATORY STUDIES HELP EXPLAIN CLINICAL COURSE OF SYPHILIS

Some National Institute of Allergy and Infectious Diseases grantees have reported data supporting the hypothesis that the unusual clinical course of syphilis is due to a general suppression of cellular immunity. The investigators found that lymphocytes (white blood cells) from syphilitic patients do not respond normally *in vitro* to trepenomal (the class of organisms to which the bacterium causing syphilis belongs) or to non-trepenomal antigens.

Untreated syphilis waxes and wanes for weeks and months before culminating in a latent stage. It has been suggested that this progression -- unusual in an infectious disease -- is due to a balance between development of the infection and suppression of immunity. Circulating antibodies, specific for the causative organism, *Trepenoma pallidum*, are present throughout the course of the disease, suggesting that defective humoral immunity is not responsible.

The grantees first extended earlier studies which had suggested that inhibition of lymphocyte response to nontrepenomal antigens may be generalized during syphilitic infection. Blood samples were obtained from syphilitic patients after their disease had been diagnosed but before antibiotic treatment had been initiated. Blood was also drawn from non-syphilitic persons matched for age, sex, race, and approximate socioeconomic status.

When lymphocytes from these blood samples were exposed to substances known to stimulate cell division and to mumps and monilia skin test antigens, there were significant differences in response between syphilitic and non-

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syphilitic samples only for the two antigens. These results indicate that the cells from syphilitic patients were able to divide normally but did not respond normally to the nontrepenomal antigens.

In the second part of their investigations, the scientists exposed lymphocytes from patients and non-patients to *T. pallidum* and to two related organisms, *T. refringens* and *T. reiter*. For all three organisms, the degree of stimulation was two to three times greater in normal lymphocytes than in those from syphilitic patients.

Although the investigators discuss several possible explanations for the results they observed, their present concept of the immune response to syphilis involves both humoral and cellular factors. They believe, however, that cellular immunity fails to develop or is suppressed for some time until unknown factors supervene, leading to an effective cell-mediated response that ushers in the latent period.

Daniel M. Musher, Ronald F. Schell, Ronald H. Jones, and Alice M. Jones of Baylor College of Medicine and the Veterans Administration Hospital, Houston, and the Florida Institute of Technology Medical Research Institute, Melbourne, Florida, reported results of their research in the June 1975 issue of *Infection and Immunity*.

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Research Advances

FACTOR MAY ENABLE PHAGOCYTES TO RECOGNIZE BACTERIA

Chemists at the National Institute of Dental Research (NIDR) report that small peptide fragments of proteins which include N-formyl methionyl strongly attract neutrophil and macrophage scavenger cells. The scientists also find that the same peptides having non-acylated methionine are not chemical attractants.

Bacterial proteins are synthesized with N-formylmethionine whereas proteins of higher life forms with nuclei in their cells almost always are made with non-acylated methionine. The investigators believe some form of the former may prove to be a "recognition factor" that triggers the body's first line of immune defense against infections. Minute amounts of substances containing N-formylmethionine could induce white blood cells to congregate at places where bacteria have entered the body. Macrophages and neutrophils could then engulf and destroy the bacteria. Macrophages also could induce other white cells to form antibodies and set a variety of secondary immune defenses in motion.

NIDR's Elliott Schiffmann, Ph.D., Barbara A. Corcoran, B.S., and Sharon M. Wahl, Ph.D., suspected that leucocyte-attracting N-formylmethionyl peptides derived from newly synthesized bacterial proteins might be found in the culture medium when *Escherichia coli* was growing rapidly. They purified a cell-free extract of such a medium and compared its activity with that of C5a, another chemical attractant derived from one of the serum complement factors. They also tested the attractiveness of several synthetic acylated and non-acylated

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peptides.

The scientists put rabbit white cells in a non-growth medium in the upper half of a special chamber. A fine filter separated the medium from more medium in the lower half to which they added the various test substances. After a few hours, the filters were stained and studied microscopically to learn how many cells had migrated to the underside.

The investigators learned the following: only acylated forms of methionine were attractive; compounds containing formyl were more attractive than those without; larger di- and tri- peptides were more effective than single peptides, and non-polar, hydrophobic molecular properties improved attraction. They also noted that when they put N-formylmethionine in the upper chamber, test substances no longer attracted cells. Therefore, they believe that N-formylmethionine competes with other attractants by blocking a common receptor site on the cell surface.

Since both C5a and the unidentified bacterial attractant cause neutrophils and macrophages to release destructive inflammatory lysosomal enzymes, and since investigators elsewhere report that so do formylmethionyl peptides, the chemists suggest that some formylmethionyl compounds might be clinically useful to reduce undesirable inflammation.

They reported their findings in the *Proceedings of the National Academy of Sciences*, March 1975.

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NEWS & FEATURES From NIH September 25, 1975

Photo Feature

POSSIBLE EFFECTS OF AEROSOLS ARE EXPLORED

The widespread use of the aerosol "spray can" dispenser has resulted in a possible human health hazard, including the potential for interfering with certain heart functions.

The spray dispenser has made available a great variety of complex materials in respirable form. While the acute toxicity of many of the active ingredients in such dispensers has been investigated, little is known about the chronic toxicity of these compounds, or the toxicity of combinations of these compounds and the inert ingredients of the pressurized cans.

In studies by Robert T. Drew, Ph.D., of the National Institute of Environmental Health Sciences, exposure of rats, rabbits, and hamsters to aerosols of aluminum chloride-hydroxide, a constituent of virtually all deodorant sprays, have produced increases in lung weights and damage to air passages in the lungs. Some of the fluorocarbons (Freons), which are the propellant gases and solvents in aerosol sprays, have been shown to depress certain heart functions, such as the contractility of the normal heart muscle. In addition, toxicity studies in progress indicate that certain chemicals in widespread use may be highly toxic to animals with pre-existing heart disease or respiratory imbalance.

The number and variety of toxic substances released into the environment as a result of modern technology increases year by year. Because of the nature of our society, we become more and more dependent upon technology for jobs, transportation, control of diseases, production of food, fiber and energy, and the preservation of foods and material. No segment of the population can escape some contact with potentially dangerous substances.

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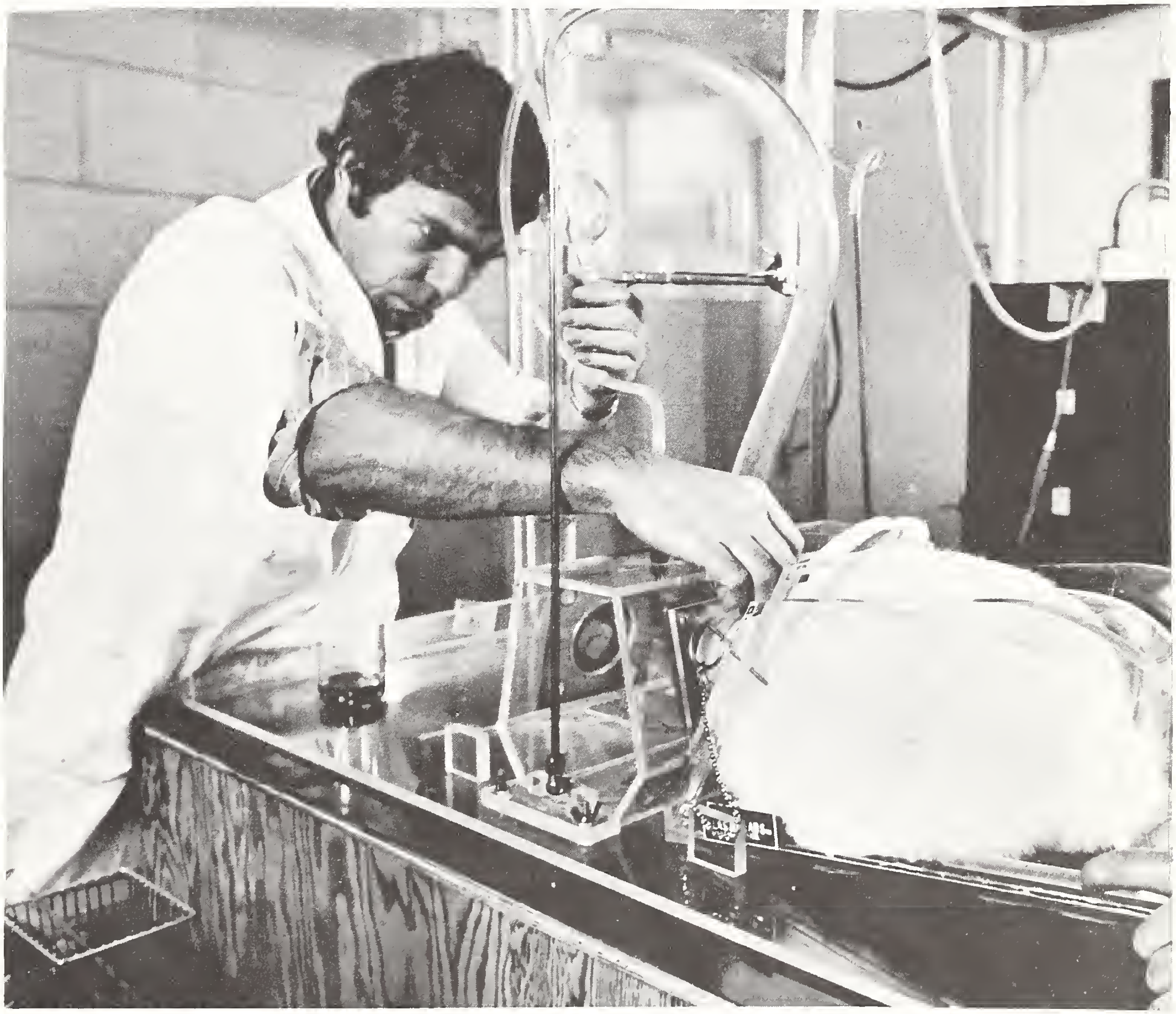
AEROSOLS (Cont'd)

It is imperative, therefore, as recent history has often demonstrated, to identify potentially dangerous agents in the environment, or proposed for future release, and to understand the consequences of human exposure to them in terms of overt and covert diseases and physiological disorders. Knowledge is the first defense against further degeneration of environmental quality with its consequent toll on the quality of human health.



This rabbit, in a plastic hutch, is being prepared for an experiment to test various effects of an aerosol spray. (NIH Photo #1460)

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News Feature

OPERATING MICROSCOPE AIDS IN TREATMENT OF STROKE

Progress in the treatment of cerebrovascular disease (stroke) is based on many small but significant improvements rather than any striking advances. Treatment varies according to the stage of the illness and the type of problem encountered. No one new procedure or development is expected to affect the prospects for all patients, but a recent report by the National Institute of Neurological and Communicative Disorders and Stroke provides a measure of progress and a generally optimistic outlook.

In the past, cerebrovascular surgery has been limited almost entirely to correction of flaws or blockages (aneurysms, malformations, etc.) in the larger arteries such as the carotid arteries in the neck, which are relatively accessible. In recent years, intracranial arteries have come within reach of the surgeon. With the operating microscope, it is possible to remove clots from very small vessels, and also to make grafts of very small blood vessels (down to one millimeter in diameter) in order to bypass aneurysms and provide collateral circulation.

Of special interest have been recent attempts to channel blood into the brain from the scalp arteries, through holes drilled in the skull. Nearly 400 patients, mostly in Europe, but some in the United States, have undergone this procedure. The Institute's Section on Head Injury and Stroke, in collaboration with the National Naval Medical Center, has reported from animal studies the effects of these grafts on regional cerebral blood flow and on its autoregulation, and have measured significant increases in blood flow and persistence of autoregulatory mechanisms despite some instability.

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However, this technique is still experimental and will require careful evaluation before it is introduced into routine medical practice.

A novel approach to the surgical treatment of cerebral aneurysms and other vascular defects was reported recently by grantees at Massachusetts General Hospital. These investigators have been experimenting with powerful magnets, which are used to guide catheters into small branches of the cerebral arteries that are otherwise inaccessible. So far limited to animals, the work has demonstrated that artificially-produced aneurysms can be thrombosed--or plugged--with detachable silver plated catheter tips, and that the tips can be held in place magnetically until clotting seals off the aneurysm.

This group also is working with ferrofluid--a carrier liquid containing extremely small particles of an iron compound. The ferrofluid can be fed into aneurysms via a catheter, and then held there by an external electromagnet until the aneurysm is filled and sealed off by fibrin and clotted blood. The procedure, if successful in humans, could replace major brain surgery for many patients with arteriovenous malformations and carotid cavernous fistulae as well as aneurysms, and could very favorably affect patient survival as well as health care costs.

A broad-scale search continues for better drugs for treating cerebrovascular disease. Anticoagulants are commonly used in non-hemorrhagic strokes, as are blood pressure lowering agents. Efforts are being made to evaluate clot dissolving (thrombolytic) agents, and drugs that relax the brain blood vessels and allow them to open to their fullest diameter (vasodilators). Several drugs now are given to control the edema following strokes, and anesthetics have been used successfully to control the arterial spasms

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following subarachnoid hemorrhage.

Drugs that reduce the tendency of blood cells to stick to one another, including one of the most familiar drugs in existence--aspirin--are being increasingly studied. The chemical mechanism whereby aspirin inhibits platelet aggregation remains to be elucidated, but grantees at the Mayo Clinic in Rochester, Minnesota, are exploring a number of hypotheses. One is that aspirin acts by combining chemically with the platelet membrane; another is that it combines with one or more plasma proteins, which in turn affect platelet function. A third hypothesis is that aspirin inhibits an enzyme in the membrane, and it also is considered possible that it inhibits synthesis in the platelets of several hormones.

The Mayo scientists now are separating various blood and blood cell components in order to identify the fraction or fractions that take part in aspirin's action. The work could have great importance in leading to better understanding of the mechanism of clotting, which occurs in the majority of strokes.

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ZPG--Zero Population Growth is reached when a population neither increases nor declines over a period of time--that is when the number of births and immigrants is balanced by the number of deaths and emigrants, according to the National Institutes of Health.

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News Feature

THERAPY COMBINATION USED FOR RHEUMATOID ARTHRITIS

A recent study conducted at the University of Colorado indicates that low dose cyclophosphamide plus prednisone is effective in suppressing disease activity in patients with rheumatoid arthritis (RA). The treatment of severe RA with high doses of cyclophosphamide is beneficial, but is associated with an increased incidence of adverse reactions, while low doses of the cytotoxic agent are often of little benefit. Scientists showed that the combination of low dose cyclophosphamide and prednisone has clinical benefits and few side effects in patients with RA.

Charley J. Smyth, M.D., a grantee of the National Institute of Arthritis, Metabolism and Digestive Diseases, and fellow associates at the University of Colorado conducted comparison studies of high dose cyclophosphamide therapy and treatment with low dose cyclophosphamide plus prednisone.

They administered cyclophosphamide orally in high doses to patients with RA for six months. Subsequently, another group of patients received low doses of cyclophosphamide plus low doses of prednisone for six months in a controlled study. The investigators measured joint function and joint inflammation to estimate disease activity.

Although joint inflammation progressively decreased and joint function improved in the patients on high dose cyclophosphamide therapy, the clinical improvement was associated with frequent toxic reactions. In contrast, the patients under low dose cyclophosphamide plus prednisone therapy had similar clinical improvement, but with fewer immediate toxic reactions. The researchers report, however, that further study is needed to determine the

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long-term serious side-effects of the combination therapy as well as whether the low toxicity of the treatment results from the lower doses of cyclophosphamide or from the concomitant use of prednisone.

The investigators published their findings in the *Archives of Internal Medicine*.

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HEPATITIS--Viral hepatitis occurs in at least two distinct forms. A person acquires hepatitis A, or infectious hepatitis, by direct contact with an infected person or by contaminated food or water. The virus of hepatitis B, or serum hepatitis, is usually transmitted by the transfusion of blood or inoculation of blood products from infected persons. Recent evidence indicates that yet another agent, or agents, may also cause post-transfusion hepatitis. A major research effort is under way at the National Institute of Allergy and Infectious Diseases to increase understanding of the causes of hepatitis and to hasten vaccine development and production.

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NEWS & FEATURES From NIH September 25, 1975

Research Illustrated

NEWBORN MONKEYS RECEIVE SPECIALIZED ATTENTION

Nursery procedures at the Oregon Regional Primate Research Center, which is supported by NIH's Division of Research Resources, depend upon a good working liaison between the medical staff, the breeding supervisors, the colony supervisors, and the principal investigators who use the nursery facilities for the welfare of the animals and the success of the research project. The neonate's first day in the nursery is usually critical, and the infant is frequently observed by the attendant paying particular attention to respiration, general appearance, and the umbilicus. Because a neonate is born with little or no thermo stability, the newborn is placed in a preheated incubator about 85°-90°. Since respiratory disorders require instant attention, 100 percent oxygen and suction units are available at all times, in addition to a stand-by incubator heated and ready for emergency use. The most important maxim of care is that a newborn infant should have a minimum of handling and a maximum of observation. The nursery infant's rate of body weight gain and body size are about the same as that of an infant reared by its mother. (NIH Photo #1461)

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Note to Subscribers:

Joyce C. Flaherty assisted in the preparation of this story.

At first, an infant in the nursery may refuse food, especially if it has been nourished by the mother. However, after three to four hours the infant accepts milk readily. For the first two days it is sometimes necessary to feed the infant with a syringe, but the bottle is always introduced at each feeding. (NIH Photo #1462)

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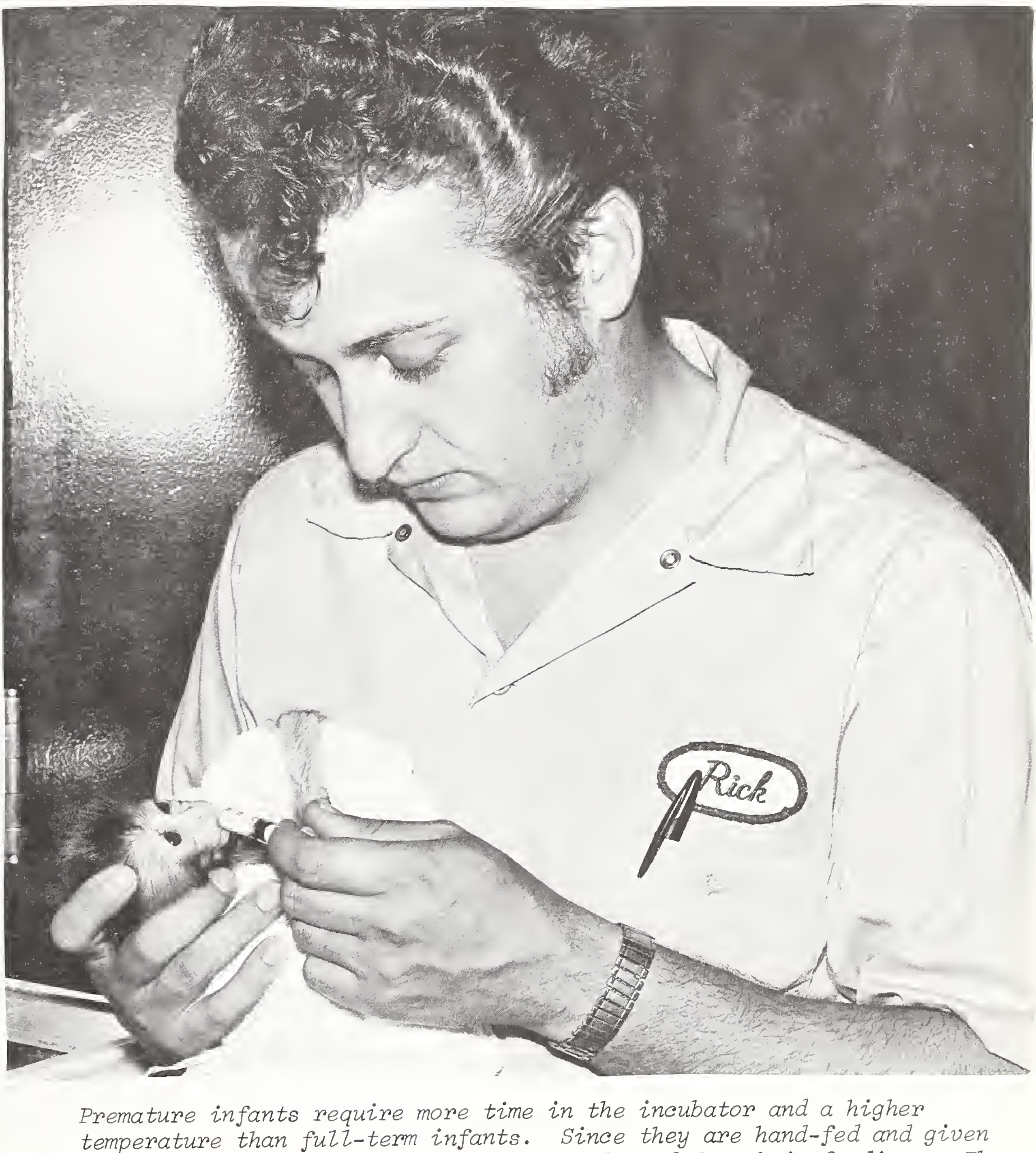
RESEARCH ILLUSTRATED (Cont'd)



Premature infants require more time in the incubator and a higher temperature than full-term infants. Since they are hand-fed and given smaller amounts of food, more time is allotted for their feedings. These infants are observed more closely, even a slight weight loss often leads to more serious trouble in a short time. In this photo, Rick Jones hand feeds a premature 25-day-old infant with a syringe. Its weight increased from 306 grams at birth to 393 grams at the end of the first month. (NIH Photo #1463)

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RESEARCH ILLUSTRATED (Cont'd)

A feisty infant finally gives up (or in) to Arthur S. Hall, D.V.M., Head of Animal Sciences at the Oregon Regional Primate Research Center. Even though some infants need a little help in adjusting to their new environment, this one proved he still had lots of ginger. *(NIH Photo #1464)*

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The nursery infant's rate of body weight gain and body size is about the same as that of an infant reared by its mother. Each infant is weighed daily at about the same time. Weighing time affords the best opportunity to examine the infant and to report any unusual conditions to the supervisor. (NIH Photo #1465)

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Since removal of the infants from the incubator to individual cages usually occurs around two weeks of age, it can be critical for the animals, so they are observed closely for signs of dehydration and diarrhea. They are housed in all-wire cages, 22" high x 19" wide x 18" deep, which enable them to see and touch one another. The cages are cleaned daily. (NIH Photo #1466)

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During the period of time just before the infant is scheduled to leave the nursery, it is housed in a larger group cage along with ten to 20 other infants. This provides a period of social adjustment during which the infant is carefully observed for signs of maladjustment, including abnormal eating habits, drinking habits, and diarrhea. This is the first time the infants experience a completely solid diet and competition in obtaining food. (NIH Photo #1467)

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NEWS & FEATURES From NIH

September 25, 1975

Disease Profile

MOUTH CANCER MAY SPREAD TO LYMPH NODES IN NECK

Cancer of the mouth accounts for about four percent of all cancers that occur annually in the United States. Usually it can be detected in early stages by routine examination of the mouth by a dentist or physician. Sometimes mouth cancers are first detected by persons who are alert to sores or lumps that do not clear up quickly, and bring them to the attention of their physicians. Cancers detected and treated in early stages usually have the best chance for cure, according to the National Cancer Institute.

Mouth cancer can occur in men and women of any age, but most frequently is found in men after age 40. Cancer of the tongue accounts for about 20 percent of all mouth cancer, and cancer of the salivary glands, 10 percent. Cancer of the lip accounts for approximately 15 percent. About 25 percent are pharyngeal cancers which affect that part of the alimentary canal between the mouth and the esophagus. Other sites include the floor of the mouth, gums, palate tonsils, lower jaw, and cheeks.

Cancers of the mouth, including the pharynx, cause about 8,000 deaths annually in this country. However, more than half of all mouth cancer patients are alive five years after treatment. Eighty-eight percent of men treated for lip cancer are alive five years later, but only 28 percent of those treated for tongue cancer survive more than five years.

Regardless of site, mouth cancer, like all cancer, is an uncontrolled, irregular growth of cells. Normally, cells proliferate to build new tissue sufficient for the growth of an organism or the repair of an injury. When this process becomes disordered, cells reproduce uncontrollably, building

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up masses of excess tissue called tumors. Cancers are malignant tumors that extend into adjacent tissues or organs, or spread to other parts of the body through the blood or lymph channels. In mouth cancer, the malignant cells may spread to the lymph nodes in the neck.

Unusual conditions in the mouth, lips, or tongue may be signs of cancer. The most common is a sore that fails to heal, bleeds rather easily, and may or may not be painful. Other signs may be a lump or thickening, whitish patch, sore throat, bleeding, difficulty or pain in chewing or swallowing food, or the sensation of something in the throat. There may be restricted movement of the tongue or jaws, discomfort in wearing dentures, or pain. Symptoms that may appear outside the mouth are a lump or swelling around the ear or in the upper neck, a sore, or facial paralysis. Any such symptoms should be reported to a physician.

Mouth cancer, like any other cancer, is diagnosed by biopsy. In this simple surgical procedure, a small piece of tissue is removed from the suspected site and examined under a microscope for abnormal changes that indicate malignancy, or cancer. As a preliminary or screening step, many dentists and physicians now take a cytologic (cellular) specimen by scraping cells from a suspicious area for examination under a microscope by a pathologist.

This test is not a substitute for biopsy; if the smear shows signs of cancer, a biopsy is done to confirm the diagnosis. Study after study has shown, however, that routine oral cytologic examination has a high potential for ultimately reducing the death rate from mouth cancer through early detection.

Many patients delay getting medical attention for mouth lesions because

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these conditons are so common. But most mouth cancers grow and spread quickly. For the most effective treatment, early diagnosis is essential.

Surgery and radiation are the principal methods of treatment, the choice depending on the site and stage of the disease. Sometimes either form of treatment may be used effectively, and often one is used to supplement the other. For example, radiation is sometimes used to shrink tumors of the cheek or floor of the mouth before surgery.

The source of radiation may be external, such as radium in a mold that fits the area to be treated, X-rays, or cobalt-60. Radium needles may be implanted to treat some cancers of the upper lip, tongue, cheek, or floor of the mouth. External radiation may precede this operation.

When surgery is the method of treatment, the lymph nodes in the neck are often removed with the primary cancer. These nodes, into which the lymph system of the mouth drains, often trap spreading cancer cells. Their removal may help prevent further spread.

To help ensure removal of all malignant tissue, extensive or "radical" surgery may be necessary in some cases. Although such procedures are sometimes disfiguring, highly developed techniques of reconstructive surgery can be used to rebuild or repair facial features or other affected areas. If a complete reconstructive procedure is not advisable at the time of cancer surgery, temporary artificial devices of a cosmetic nature can be employed.

Although scientists do not yet know what causes mouth cancer, they have identified many factors that contribute to its development.

A long-suspected association between tobacco and mouth cancer was

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confirmed in 1964 by the Advisory Committee on Smoking and Health appointed by the Surgeon General of the Public Health Service. According to the Committee's report, this relationship was first suspected in the early 18th century, when lip cancer was noted among tobacco users. In modern times, many studies have shown a significant link between mouth cancer and the use of smoking or chewing tobacco, or snuff. Several studies showed that the death rate from mouth cancer is about four times higher for cigarette smokers than for nonsmokers.

Mouth cancer is also strongly linked with pipes and cigars. The Committee noted that pipe smoking as a cause of lip cancer seems to be established. It also reported that the heat from burning tobacco has not been sufficiently investigated, and may be a factor in the high rate of lip cancer among cigar and pipe smokers.

Chronic irritation, such as that caused by sharp, jagged teeth, projecting fillings, or badly fitting dentures, should be avoided and its cause promptly corrected by a dentist. This obvious reason is to relieve discomfort, but it is also possible that chronic irritation might lead to the development of cancer.

Among farmers, sailors, and other outdoor workers, exposure to sunlight over many years sometimes results in lip cancer. Excessive exposure over the years to wind and frost also may be a contributing factor.

Excessive drinking of alcohol with or without tobacco use appears to play a role in the development of mouth cancer. Although heavy drinkers are

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often heavy smokers, the relative contribution of the two factors to the causation of oral cancer has not been determined.

Certain non-cancerous mouth conditions that tend to become malignant include leukoplakia of the mouth, some tumors, and a tissue wasting disease called Plummer-Vinson syndrome. Leukoplakia is a rather common disorder in which a painless white patch of cells forms on the lip, tongue, or mouth lining. If leukoplakia does not disappear, it should be biopsied and checked regularly. Some physicians believe that white patches and benign tumors, such as papillomas, should be removed.

Plummer-Vinson syndrome, a wasting-away of mucous membranes of the mouth, pharynx, and esophagus caused by deficiencies in the diet, frequently precedes mouth cancer. It is common among women in Sweden and apparently accounts for their unusually high incidence of mouth cancer.

Much research on cancer of the mouth is directed to improving treatment. For example, many physicians are investigating a method of pumping drugs through the veins of the head and neck in order to reach the affected area directly and slow the course of the disease. Initial results from one group of investigators are encouraging. However, at present, drug treatment offers only temporary relief.

There is need, too, for research on methods that will assist physicians in detecting mouth cancer in the early stages. As research continues to produce new information that may be applied to management of cancer, the outlook for persons with mouth cancer and other forms of the disease can be expected to improve.

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